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RESEARCH OF THE SCIENTIFIC LITERATURE AND REPORTS ON THE EFFECTS ON MAN OF ALCOHOL ALONE AND IN COMBINATION WITH OTHER DRUGS

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FOREWORD

This is a final report prepared under contract AF 41(609)-1590 (Project 8241, Task 824133) with The Hine Laboratories, Inc., San Francisco, California. This report covers research carried on from May 1962 to May 1963. Air Force program monitor is Dr. Horace F. Drury, ALR, Arctic Aeromedical Laboratory.

Research personnel include Marjorie L. Dewey, Mary L. Fraser, Emily L. Spalding and V. C. Sutherland. References reviewed for this report are contained in a 15 volume set, with an author and subject index. A set of these references is located at -- Library of Congress, Technical Reports Division, Washington, D. C. 20540; National Institutes of Health Library, Division of Research Services, Bethesda, Maryland, 20014; National Library of Medicine, Technical Reports Division, 8600 Wisconsin Ave. Bethesda, Maryland, 20014 and the Library of the Arctic Aeromedical Laboratory, Fort Wainwright, Alaska.

This technical report has been reviewed and is approved.

Horace F Drury

HORACE F. DRURY
Director of Research

ABSTRACT

This review of medical and scientific literature was undertaken to establish what knowledge was existent regarding effects of alcohol and other drugs in the presence of reduced environmental temperatures on the behavior of animals and man. The gathering, classifying, and reviewing of this literature was necessary to determine whether further work should be done in this area. The paramount problem was to determine whether reduced environmental temperatures such as might be expected in environments in which Air Force personnel would be operating in their world-wide mission were a factor which should be considered in predicting behavior, following the ingestion of alcohol, taking of drugs or exposure to other agents which might have effects on the central nervous system. This review was accomplished in part by direct reference to journals dealing with the action of drugs and environmental agents, and in part by reference to standard abstracting sources. Special attention was paid to material appearing in the Quarterly Journal of Studies on Alcohol. Wherever the subject matter seemed of sufficient importance to require critical review of original data, the original articles were sought out and analyzed. In all, more than 4, 500 articles and abstracts were read. Of these, 1200 were selected as being especially pertinent and 700 of these were carefully reviewed. A cross-index was prepared according to major topic headings. Due to the paucity of material pertaining to the subject of the environment, the original scope of the project was enlarged to consider information which would be requisite to an experimental investigation of the problem. Special attention was directed toward the pharmacology, physiology, effects on the nervous system, and behavior following acute or repeated intake of alcohol. Numerous observations have been made regarding the effect of alcohol alone. Relatively few have been made concerning the combinations of alcohol with other drugs. Practically no information was available concerning the effect of the environment, drugs and chemicals, especially as regards reduced temperatures. Based on the literature review, a narrative description of the material necessary to evaluate the original problem was made and recommendations were set forth for an experimental program which would obviously have to be carried over some period of time in order to clarify the many undetermined factors relating to the effects of alcohol alone and in combination with other drugs as influenced by reduced ambient temperatures.

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I

INTRODUCTION

In preparing this review we were struck by the diverse nature of the reports which appear in literature concerning acute alcohol intoxication. As judged by the total number of reports, this subject has been investigated by a tremendous number of pharmacologists, biochemists, clinicians, psychologists and toxicologists. Unfortunately, many of the experiments lack objectivity, are poorly designed and contain too few observations to support the conclusions reported.

There were surprisingly few studies on the action of alcohol in combination with other drugs affecting the central nervous system, but from the available information it will appear that while other drugs may potentiate the effects of alcohol, none of them have any real synergistic effects. There was relatively little information concerning environmental factors which influence the action of alcohol on either experimental animals or human subjects, and there is obviously a need for a considerably greater amount of research in this area. An excellent review of the general effects of temperature on drug action has been made by Fuhrman (1, 2) though there are relatively few references to alcohol itself. In developing this report we purposely extended our activities beyond the principal charge of developing information relative to the effects of alcohol alone or in combination with other drugs on the nervous system, since we believe that information relative to the diagnosis of intoxication, the medicolegal significance of inebriation, and the addicting properties of alcohol, are subjects of considerable significance to the Air Force.

Characteristics of Alcohol

Ethyl alcohol, grain alcohol, ethanol, C_2H_5OH, is a colorless mobile liquid of pleasant odor with a flash point of 12° C and a vapor pressure at 20° C of 44 mm Hg. Completely miscible with water, it has a boiling point of 78.3° C, a density of 0.7894, and as commercial alcohol of 95.7% by weight forms a constant boiling mixture with water of 78.2° C. Approximately 700,000,000 proof gallons of ethyl alcohol are produced in the United States annually, the majority of this through fermentation processes. The allocation of ethyl alcohol for industrial purposes indicates that over half is used for the production of synthetic rubber, 20% for intermediate chemical manufacture, 7% for solvent use, and the rest for a wide variety (over 300) of applications and manufacturing processes. Synthetic alcohol is made by hydrolysis of ethyl sulfuric acid which is formed through the

hydration of ethylene or acetylene. Since antiquity it has been manufactured through the fermentation of sugar or starches of various sources in the presence of yeast. Raw material includes molasses, grains, corn, sorghum, rye, barley, pineapple juice, whey. Despite its wide industrial use, its social implications and man's behavior secondary to its use are the reason for this review.

Background

The history of the use of alcohol is as old as the history of man, being closely interwoven with religious myth, fertility rites and social customs. The story of Noah is reported to represent the discovery of alcohol. The ancient Egyptians attribute the discovery of wine to Osiris, and in Chinese tradition the maid, Yi Tieh, produced it "de novo" about 2000 years B.C. as drink for the harassed emperor Yu. The relief of anxiety and the dissipation of tension, and the mildly sedative and relaxing action of moderate doses of alcohol is today the basis for the persistent use in most societies throughout the world. The ancient Greeks credited Bacchus with the transmission of the art of wine making to man. Alcohol as obtained by distillation was probably first discovered by the Arabian alchemists, and hence the Arabic name of "Al Kohl". The word "Kohl" came to denote a fine powder, the name given eventually to all sublimates and distillates.

Baume in 1773 (3) describes in his "Chymie Experimentale", a distillation of the liquid for use in chemistry and medicine, but it was not until this century that these highly alcoholic liquids were used as drink. Alcoholic beverages contain varying quantities of alcohol, and for general orientation purposes a summary of these follows:

TABLE I

Approximate Alcoholic Content of Various Beverages

Name	Percent of Alcohol by Volume
Very light beers	2.0-3.0
Light beer	3.5-4.0
Stronger beers, porter, stout, ale	4.5-6.0
Cider	4.5-5.5
Table wines -- light	6.2-12.0
Vintage wines	8.0-9.0

TABLE I (cont'd)

Name	Percent of Alcohol by Volume
Effervescent wines and champagne	9.5-10.5
Sherry, port	14.0-20.0
Liqueurs	30.0-50.0
Brandy and gin	35.0-40.0
Cherry brandy Cognac Whisky	48.0-50.0
Rum	50.0-69.5
Chartreuse (green)	50.0-60.0
Vodka	60.0-80.0

Medical Uses

As reported by Goodman (4) alcohol and alcoholic beverages are used widely for numerous ailments by the laity, and their legitimate uses in medicine are difficult to describe. Certainly alcohol is an excellent solvent and has been used as such for many drugs, frequently being employed as a vehicle in medicinal mixtures. A cooling sensation is experienced when alcohol is allowed to evaporate from the skin and it is used for this purpose in fevers. It is also contained in liniments because of its rubefacient properties. Since it decreases sweat it is an ingredient of anhidrotics and astringent lotions. It is frequently used as a popular skin disinfectant, and because it is bacteriologically potent in a concentration of 70%, is widely used as a sterilant. It is not used to disinfect wounds or raw surfaces because it is neutralized by proteins. Reports in the recent medical literature indicate that it was reevaluated extensively as an anesthetic hypnotic and analgesic in the period 1940-1960 with varying degrees of enthusiasm.

When used intravenously during childbirth, alcohol levels may reach .12 to .18%, thus rendering the majority of patients fairly comfortable. The alcoholic concentration of fetal blood immediately after delivery is approximately 20% lower than the mother's. These blood levels were not noted to produce any change in the baby or interfere with spontaneous

initiation of respirations. However, in 100 unselected obstretical patients the intravenous administration of 7.5% ethyl alcohol resulted in varying tolerances, requiring individual adjustment of the rate of administration. Analgesic effects were excellent at a concentration of alcohol of .065% in the venous blood of mothers. Ethyl alcohol has been used successfully as an analgesic, euphoric, anti-pyretic and vasodilator in the treatment of phantom limb pain, peripheral vascular disease, pyrexia, and intractable pain. Treatment of opium addicts in which substitution was made over a period of six days was reported as highly successful. Success has been reported also when alcohol was used as an agent for quieting patients in a state of exhaustion in some forms of mental disease, including manic-depressive psychoses, schizophrenia and catatonia, especially when patients were in extreme exhaustion with dehydration.

Alcohol has been sometimes used to increase appetite, as a hypnotic in insomnia, and in certain peripheral vascular and coronary artery diseases. It is contraindicated in ulceration of and hyperacidity in the gastrointestinal tract, epilepsy, acute infections of the urinary tract, or in patients who are inclined to become addicted.

When alcohol is administered post-operatively, in addition to a beneficial effect on nutritional requirements, other advantages include the well-being of the patient, the elimination of the use of morphine, and a concomitant decrease in the incidence of paralytic ileus in gas pain. Given intravenously ethyl alcohol provides quickly utilizable food, spares carbohydrates and fats, and permits utilization of protein for anabolism. As an analgesic it raises the pain threshold and produces indifference to perceived pain. It reduces the use of opiates, is beneficial in terminal patients, in asthenia, and in post-operative delirium tremens.

According to reports in the Russian literature, when local anesthesia cannot be used, ethyl alcohol anesthesia is a method of choice. The average dose for complete narcosis is between 2 and 2.5 cc/kg of body weight. The alcohol is administered with 2 parts 5% glucose, and the resulting sleep generally lasts 2 to 5 hours. A synergistic action of alcohol and hexanal (a barbituric acid derivative) has been utilized to advantage in intravenous anesthesia. This procedure prolongs the narcosis. The chief advantages to alcohol anesthesia as recorded by the Russians are the ratio between the narcotic and toxic dose, the reversible effect upon tissues, the pleasant aftereffect, its acceptability in patients with respiratory complications, its lack of expense, easy preservation, and non-explosibility in the surgical area requiring open flames. The chief complications are phlebitis of the veins when administered in the extremity, and excitement occurring after sleep.

The administration of ethyl alcohol has been proposed by Roe (5) as an antidote for methyl alcohol poisoning, based on the theory that ethyl alcohol has a greater surface activity on the enzyme receptor than does methyl alcohol, and the latter therefore becomes displaced from enzyme surfaces and thus the oxidation of methyl alcohol and the production of formic acid is inhibited. However, the accompanying acidosis must also be corrected by alkaline salts. The post-operative use of a solution containing 7.5% ethyl alcohol, 5% protein hydrolysate and 5% dextrose in 1000 cc of water is reported to minimize nausea, provide a good substitute for opiates, and not be accompanied by respiratory depression. The solution relieves anxiety and tension, provides calories, sedation and analgesia, and no systemic or allergenic reactions have been noted in a series of over 500 patients.

Brown (6) reported on successful treatment of 5 of 6 patients in status asthmaticus by the intravenous injection of ethyl alcohol, and concluded that this treatment fulfills all the essential criteria of an ideal drug for this situation.

Intravenous alcohol infusions are certainly contraindicated in demonstrable liver damage or history of epileptic attacks, and despite the favorable reports, the Council of Pharmacy and Chemistry in 1948 refused to approve the preparation of 5% ethyl alcohol as a combined analgesic and caloric provider for post-operative states. Evidence advanced in support of the preparation, including the use of alcohol for intravenous infusion as a sedative and as an adjunct in the treatment of certain diseases including delirium tremens, was found to be poorly documented and therapeutic evidence unconvincing. It was indicated that the peripheral vasodilatory effect would be deleterious in the presence of shock or impending shock, and although alcohol may be useful when other narcotics are contraindicated, it is subject to the production of tolerance, leaves much to be desired as a sedative, and is a feeble stimulant in respirations.

Ethyl alcohol is probably contraindicated in most hepatic and renal disease, and in infections of the lower urinary tract. The medical use of alcohol in a particular disease state should be at the discretion of the physician and individualized for that case. It has had an application for years in the injection about regional nerves as a procedure for the relief of pain not obtainable by other measures. It has a long and well-accepted position as a stomachic to improve appetite and digestion. Its use as an anti-foaming agent in the treatment of pulmonary edema has been reported as favorable due to its surface action; however, it is probably not as efficient in this area as the newer synthetic agents.

Consumption of Alcoholic Beverages

According to Dr. Greenberg (7) there are some 80 million adults in the United States who drink beverages containing alcohol under a multitude of different occasions and in different degrees of moderation. A Gallup Poll conducted in May of 1960 reported that beer, wine or hard liquor is occasionally consumed by 62% of the American population. A New York survey in 1958 showed that 71% of householders served alcoholic beverages within the month preceding the inquiry. In 1950 there were an estimated 40 million male users of alcoholic beverages in the United States, equal to 26% of the total population. The total consumption of absolute alcohol by this group was 181,000,000 gallons, or 80% of the total. The consuming male population may be divided into three population groups consisting of 3,276,000 alcoholics who each consumed an estimated 8 ounces of alcohol daily, 7,300,000 moderate drinkers who consumed daily an average of 3.5 ounces of absolute alcohol, and 28,654,000 occasional drinkers who consumed less than .5 ounce daily.

It would appear that in the United States the major portions of alcoholic beverages are consumed by males, though statistically they are not any greater in number than female users. Drinking of alcoholic beverages, therefore, is not limited to a small group of persons. At least 2/3 to 3/4 of the population at some time drinks alcoholic beverages. About 4 Americans in 10 drink beer, and 1 in 4 whiskey once a week. Drinking varies according to age and reaches its peak in the age group between 35 and 40. Social circumstances surrounding drinking indicate it does not occur randomly throughout the day or the week, but that there are peaks for drinking centering around evening hours; weekend drinking far outweighs that done during the working week. The reason for drinking is described in terms of fulfillment of individual needs and as a result of social influences depending on the philosophic and disciplinary position of the investigator. It is certain that drinking is a complex, learned individual behavior which generally occurs in a social setting, and an individual's drinking behavior seems to reflect his early training, momentary needs, long-term psychological needs, as well as the social context in which he places himself or finds himself at the moment. A survey conducted by Riley in 1948 (8) indicates that drinking is directly motivated by the influence of social pressure as much as it is by acquired inner drives. Approximately 40% of persons assigned their main motivation to group pressures. This social pressure is more influential in the motivating of drinking by women, the young and the occasional or infrequent drinker. The social pressure is not custom, except in certain rare cases of persons who descend from particular ethnic groups, nor is it institutional, but rather the kind of transitory social pressure which characterizes much of the personal behavior of people in changing social orders, or when authoritatively sanctioned rules of behavior have not replaced old

mores and old customs. Regardless of the forces that lead to the consumption of alcohol, the intake of alcoholic beverages is a medical and social problem which is of extreme importance in our time and has far-reaching influences on both group and individual behavior. This is important to the military in terms of the increased incidence of accidents, delinquency and lower efficiency which follows acute intoxication and subclinical alcoholic intoxication, but particularly the state of chronic alcoholism.

II

ACUTE ALCOHOLIC INTOXICATION

General

Acute alcoholic intoxication is seen so frequently by the public that a detailed description of the event is probably not required. However, the commonly held belief of the public that alcohol is a stimulant due to its powers to lessen inhibition and cause impulsive behavior may need correction, though as early as 1883 the noted German pharmacologist Schmiedeberg advanced the postulate that alcohol is a depressant of the central nervous system. There is no question but that the central nervous system is affected to a greater extent by alcohol than is any other system of the body. The depression which results is an irregularly descending one and resembles that produced by general anesthetics. Particular behavior which is exhibited as a result of alcohol is a product of two factors, in addition to the degree of tolerance to alcohol, namely the psychological makeup and personality of the individual, and the environmental situation in which the intoxication is experienced. In the psychic sphere one notices a loss of the finer grades of attention, reflection, judgment and comprehension. There occurs a lack of self-criticism and incorrect assessment of one's own performance which is misleading in that the intoxicated person feels that he is performing better. At low levels of alcohol he becomes pleased at the ease with which he expresses his thoughts, his courage increases and he attributes to himself many attributes which he does not possess. As acute alcohol poisoning advances there occur noticeable changes in the general appearance which are secondary to the physiological effects of intoxication. The pupils appear to be generally dilated and the reaction to light and accommodation is sluggish. In far-advanced coma, the pupils may be small though they respond to tactile stimulation on the skin and to light. The facies are generally warm and flushed. The conjunctiva of the eyes are engorged due to the vasodilatory effects of alcohol, though there is little change in physiological factors such as blood pressure and pulse rate. There is, of course, a marked effect on muscular coordination so that there is slurred speech, impairment of gait and balance, and a

lengthening in reaction time. As the blood alcohol level increases and the degree of intoxication grows greater, there may be evidence of impairment of circulation due to interference with the airways, so that the ears and lips may become cyanosed, the face itself may assume pallor due to failing circulation, the temperature becomes markedly subnormal, breathing sonorous and irregular, and the pulse becomes poor in volume. Coma which persists for 10 hours and is not treated generally becomes fatal. As the concentration of alcohol in blood increases, the degree of intoxication decreases, though individuals vary considerably as regards the more basic physiological changes. A summary follows of the relation between the alcohol concentration in the blood, urine and spinal fluid, and the effects generally seen.

TABLE II

Certain Manifestations of Behavior in Relation to Ethyl Alcohol Levels

Effect	Mg of Alcohol		
	Blood	Urine	C.S.F.
Slight changes detectable by special tests	<50	<60	---
Beginning of uncertainty	60-80	>100	70-90
Emotional instability; decreased inhibitions, slowing responses to emergencies	80-100	>100	100-120
Slow comprehension (at this level about 30%-50% of patients are clinically intoxicated)	100		
Drowsiness / Drunkenness — Between these levels at least 50% of patients cannot be considered to be sober	120-150	135-250	130-175
	160		
Severe alcoholic intoxication; confusion; staggering gait; slurred incomprehensible speech; stupor (95% of patients were diagnosed as intoxicated on clinical examination at 250 mg%)	200-400	250-500	220-440
Paralytic coma	400-500	500-700	450-550
Death	>500	>600	550

While acute alcoholic intoxication is exceedingly common, death from uncomplicated acute alcoholism is relatively rare. Average lethal dose ranges between 250 and 500 gm of absolute alcohol. Further discussion of the effects of alcohol are reported in the section on the effects on the nervous system and the section on general physiology of alcohol. Despite the multitude of signs and symptoms, acute alcohol intoxication can be at times confused with other conditions. Moore, Alexander and Ipsen (9) have reported that intoxication with other drugs, cardiovascular accidents, mental disturbances and cerebral injury are the most common causes for diagnostic errors. Acute alcohol intoxication does contribute also to misdiagnosis of other disease states. For example, the differential diagnosis of cranial trauma and acute intoxication is an important one which can be established simply by a breath or blood test. The relevance of this can be seen from review of the records of a certain hospital which indicate that while half of 170 cases of definite head injury were judged to be under the influence of alcohol, in 5 persons no alcohol was present at all in their blood. Also, among 430 consecutive cases of head injury admitted to Boston City Hospital, 10% had prolonged confusion and 2% showed amnestic and confabulatory symptoms. Alcoholism was involved in only 21% of the total head-injury admissions, but was proven or suspected in all of the amnestic cases. Diabetic coma has in this author's experience been erroneously diagnosed as alcoholic intoxication, the true condition being readily established by biochemical tests.

Approximately 5% of all admissions during the period 1950-1953 in a General Hospital in Norway was for acute poisoning, and of this, alcoholism was responsible for approximately 12%, but the majority of other patients who had taken other drugs were alcoholics. Elevated blood alcohol levels, that is above .15%, are found in an appreciable number of suicide and accident victims. There is some disagreement as to the importance of acute alcoholism as a cause of death in the United States. According to Moore and Leary (10), it ranks second only to carbon monoxide, and the two poisons together are stated to kill more people than all remaining chemical substances and drugs. Moore and Leary relate most acute alcohol deaths as secondary to ingestion of large additional amounts of alcoholic beverages by a person already intoxicated, and point out that most deaths from "poison liquor" during the Prohibition era were simply due to overdoses of ethyl alcohol. The author's experience in 25,000 cases in the coroner's office in San Francisco is not in agreement with these findings. We have noted that while alcohol is responsible as a contributory cause in a large number of accidental deaths due to a variety of causes, lethality from the direct depressing effects of alcohol on the respiratory center is relatively uncommon. The problem is unfortunately confused with that of chronic alcoholism from which it cannot be completely separated. The latter condition is a significant cause of death, exceeding on an annual basis some types of cancer and heart disease.

Therapy

No specific treatment has been devised which is entirely satisfactory for severe acute alcoholism, and therapy is largely symptomatic. There are essentially two different regimens required, depending on the stage of inebriation. In the first instant where there is profound depression of medullary centers, the main goal is to keep the hypoxic patient in a relatively good state of oxygenation, support the depressed circulation and maintain blood pressure. Analeptic drugs are not generally any more effective in this than in the treatment of other physiological depressed states due to hypnotic and sedative drugs. Nevertheless, a large variety of central stimulating drugs have been advocated and are used. If a large quantity of unabsorbed alcohol is present in the stomach, this should be removed with careful consideration being given to the avoidance of regurgitation and resulting aspiration pneumonia. In the second condition we are faced with an individual with only moderate physiological depression, who demonstrates varying degrees of disorganization of the central nervous system. Restraint, sedation and protection are paramount. In many instances these persons are in poor nutritional states due to decreased intake of food and liquids other than alcohol. This is especially encountered in acute alcoholic episodes of the chronic alcoholic, who poses particular problems because of his physiologically unstable state with alterations in normal biochemistry. A variety of treatments have been prescribed for the management of these patients, especially those in the excitement phase who show unusual irritability of the central nervous system. A number of these treatments are reviewed.

McCrea (11) treated respiratory failure in dogs, induced by administration of large quantities of alcohol with intravenous metrazol. Spontaneous breathing occurred, and animals recovered without any effect on the disappearance rate of alcohol from blood or the duration of coma. The administration of an exchanged transfusion of 300 cc of blood has been utilized in the treatment of an acute alcohol intoxication in a child, with complete recovery. This therapy would seem drastic and has seldom been used.

Both hemodialysis using the artificial kidney, and massive infusions regulated to increase urinary output have been used in the treatment of acute alcoholism, though pulmonary and cerebral edema as well as cardiac embarrassment must be guarded against.

Davis (13) proposes that in acute alcohol intoxication, both the stagnant and histotoxic type of hypoxia occur. Since there are no figures, statistics, controls or measurements quoted in his article, and since he simply states that in 100 subjects with acute alcoholism, pure oxygen given for 20 minutes

of each hour over a period of 6 hours benefitted the subjects, the question of this type of therapy seems to remain unresolved.

Since there are frequently physiological disturbances in the acute alcoholic, such as acute endogenous and exogenous starvation coincident with the alcohol withdrawal syndrome, appropriate therapy consists of administration of glucose in saline with vitamin complexes intravenously, and solid food and fluids forced for the first 24 hours.

Following recovery from the respiratory depressant phase of acute intoxication, the four manifestations of toxicity are: psychomotor agitation, gastrointestinal disturbance, depression or anxiety, and insomnia. The treatment generally is with large doses of sedatives. Treatment of this post-intoxication state with mephenesin is reported to be successful, especially in relief of psychomotor agitation. Insomnia, a constant feature of the hangover syndrome, is not directly relieved by this compound. Other symptoms not satisfactorily treated by mephenesin alone, such as depression and anxiety, respond to amphetamine, while gastrointestinal hyperirritability and hyperhidrosis yield to atropine sulfate. The effect of the latter drug with mephenesin is reported as synergistic. As the incidence of side effects is infrequent, mephenesin is given at 1 gm dosage levels every 4 hours during the acute episode.

A number of investigators have reported that insulin and glucose will hasten recovery from acute intoxication. This has allegedly been due to an increased rate of disappearance of alcohol from the blood. While, as will be discussed later, this seems doubtful, it does appear that patients suffering from either alcoholic psychosis or acute alcoholic intoxication and treated with 10 to 20 units of insulin, may be sobered up in an average of one day, thus decreasing the normal two to four day period. No sedatives were used in this system, and patients were stated to prefer this method.

A number of different depressants and tranquilizers have been evaluated in the control of psychomotor agitation and anxiety. Paraldehyde in doses of 8 cc has long been a classical and honored therapeutic agent of use during the post-hypnotic period. Only rarely have undesirable effects and potentiation been reported. Lethality, however, has followed the unrestricted use of the material with levels of the drug in the blood and brain at the lower lethal range.

In a double blind study utilizing a check list of symptoms, the effects of meprobamate were evaluated on hospitalized and out-patient persons undergoing treatment for alcoholism. In general, meprobamate shortened the time before complete recovery, diminished the intensity of symptoms of hangover, and lowered the need for additional medication. It thus appears

to be an effective adjunct to other medications in acute post-alcoholic states. In other studies meprobamate benefitted 75% of cases during the withdrawal period. It is generally given in doses of 400 to 800 mg four times a day. Mephenesin has also been reported as improving the symptoms of excitement, confusion, incoordination and intoxication in acute alcoholic patients, so that patients will respond to this therapy in addition to routine treatment approximately one day sooner.

Chlorpromazine has proved markedly effective in producing sedation without stupor in controlling manic excitement, anxiety, psychomotor agitation and tension in the management of acute alcoholic states. Standard doses have been 100 mg of the drug on admission and 50 mg three times daily until symptoms subside. Most of the patients go to sleep for a period of three to eight hours. In a small percentage, the drug is ineffective. No synergistic effects between the drug and alcohol have been noted, even in the presence of appreciable levels of alcohol in the blood. Fazekas (13) reports that chlorpromazine in amounts of 50 mg, while producing a somnolent state in intoxicated patients, does not produce either a change in rate of oxidation or in the depression produced by alcohol. However, hypotension is found as a troublesome but readily reversible side effect. In a number of series it has been found as effective as standard treatment with barbiturates and mephenesin, the essential difference being that it quiets the patient sooner, permits him to be aroused more easily, and better controls nausea and vomiting. This has resulted in a shorter period of hospitalization than with standard treatment. Readmission rate is about the same, indicating that it has no effect on sobriety. Untoward side effects include hypotension, controlled in part by reducing dosage, and palpitation and tachycardia. Three patients so treated developed seizures and delirium tremens, and it has been suggested that patients with convulsions or impending delirium should be given, in addition, small doses of barbiturates. One fatality which may have been related to the treatment occurred in a cardiac patient with cirrhosis of the liver. Relatively few marked reactions have been reported from this drug. When chlorpromazine was given by vein, muscle or mouth to a series of alcoholics with delirium tremens, or with psychomotor agitation, sleep generally followed in 15 minutes to an hour. Acute hypertension was observed with intravenous injection; no depression of the nervous system and no synergism with the alcohol was noted; no convulsions occurred.

Prochlorperazine given intramuscularly and later orally to patients with acute alcoholism produced excellent results; there was decreased anxiety and relaxation and better sleep, which in turn helped the overall program of rehabilitation.

Dizziness and postural hypotension were encountered in the use of promazine as the only side effects in a series of acutely intoxicated hospitalized patients who presented a number of other related diseases including cirrhosis of the liver, coronary heart disease, psychoneurosis, arteriosclerosis, and malnutrition. Nausea and vomiting were checked in 90% and psychomotor agitation in the majority, following doses of 25 to 100 mg every 4 to 6 hours. When phenyltoloxamine, a relatively safe tranquilizer with some antihistamine effects, was evaluated in the potential treatment of alcoholism in skid row alcoholics it was found to have no significant effect in eight of nine alcoholics who received it, all of whom complained of continued fatigue or nervousness. Of 163 acutely ill alcoholic patients, the majority were reportedly relieved by the administration of reserpine (Serpasil) and even more strikingly by perphenazine (Trilafon). Hallucinations were well controlled within 36 hours, nervousness and tremor continued from 48 to 72 hours. Considerably less nursing care was required than when glucose and insulin were used. Major side effects included significant hypotension which occurred in 15% of the group. There seem to be no contraindications. Reserpine has been used successfully in hospitalized acute alcoholics commencing with parenteral administration of 2.5 mg followed by oral medication of .25 mg three times daily. Side effects including hypotensive reactions, excitement, tremor, and gross agitation, were well relieved within 24 hours. Combination of reserpine with mephenesin carbamate is reported as successful in slightly more than 50% of treated acute alcoholics. There is biochemical evidence of diminished function of both the adrenal and pituitary glands in acute alcoholism. Treatment with adrenal cortex controls acute intoxication in Korsakoff's psychosis, while delirium tremens and hallucinosis are reportedly successfully treated with adrenocorticotropic hormone. Both ACE and ACTH have been demonstrated by Smith (14) to be markedly effective in the treatment of acute alcoholics. ACE had a more prompt sedative effect and abolished anorexia somewhat more quickly.

Cetadiol, a synthetic steroid, is reported as especially effective in relief of withdrawal symptoms in hospitalized alcoholics. The patients were able to eat and sleep the same day treatment was begun. The total dose whould not exceed 75 mg for the period of treatment.

Vitamin preparations have been recommended for specific therapy and as a general supportive measure. Vitamin B_6 administered to acute alcoholics is reported to have a sobering effect, but to be of short duration. Fructose may be of use, since it may increase the metabolism of alcohol and has a sobering and sedative effect similar to that of Vitamin B_6 except that it appears later and lasts longer. Swedish physicians treating intoxicated patients with two doses of 125 gm of Danish honey (half of the sugar being fructose, report usually effective results, although a reported "honey-alcohol reaction" may occur which requires the injection of

antihistamines. A violent alcoholic patient given intravenous injection of 100 mg of vitamin B_6 became coherent and calm within 8 minutes and the differential diagnosis of head injury was clarified. The beneficial effects of pyridoxine has been questioned by Atkinson (15) who noted no faster recovery in parallel groups of patients, one of which received the drug in doses of 500 mg daily. Thiamine has been unduly used because of the recognized deficiency of this vitamin. Its role is discussed under "nutritional aspects".

III

PHARMACOLOGY

Absorption from the Gastrointestinal Tract

Alcohol is rapidly absorbed from the stomach and intestines, approximately 25% of an ingested dose passing through the stomach wall, though this may be influenced by the emptying time of the stomach. Agents causing pylorospasm, and large quantities of alcohol itself, increase the percentage of alcohol absorbed through the stomach but decrease the rate at which the maximum blood level is reached. The maximum concentration of alcohol in the blood usually occurs between 30 and 50 minutes following ingestion; however, in some experimental work it has not appeared for 80 minutes.

The concentration of the alcoholic beverage markedly affects the rate of absorption of ethyl alcohol from the stomach. After an original rapid absorption rate for both high and low concentrations of ingested alcohol, high concentration leads to slow absorption while low concentrations are relatively rapidly absorbed. Slow absorption is believed to be a function of delayed evacuation of the stomach. Lolli (16) carried out experiments indicating that the rate of absorption of the alcohol varies in a curvilinear manner depending on the concentration of the alcohol and the total amount given. Maximum alcohol concentration in the blood occurs following ingestion of 30% aqueous dilution of alcohol, and when taken in moderate amounts. With greater or lesser concentrations there results a lower maximal level in the blood. When alcohol is dissolved in sugared water, the resulting alcohol curve in volunteer subjects ingesting the beverage has a lower maximum which is reached later, as compared to the curve obtained after consuming alcohol in plain water. When the same amount of alcohol is drunk in the form of champagne, sweet wine or vermouth, the highest and earliest maximum alcohol concentration is obtained from champagne, and the lowest and latest from vermouth. It is concluded that the presence of sugar in the beverage lowers the alcohol concentration in the blood by slowing the absorption rates.

After the ingestion of measured amounts of different kinds of food, Rauschke (17) reported that absorption was retarded by carbohydrates and proteins and speeded up by fat. These results are in total disagreement with the observation of others that fatty foods generally decrease blood alcohol concentrations and prevent drunkenness. Alcohol administered to fasted rats gave peak levels in 15 to 30 minutes, with great consistency in the rate of absorption; unfasted rats showed a variation in the absorption rate with different concentrations of alcohol. When administered intraperitoneally, the concentration of alcohol in the blood reached a maximum level within 15 minutes. Mixing of different alcoholic drinks may affect the gustatory or olfactory centers which accelerate gastric emptying in some people and increase absorption. The same dose of alcoholic beverages given to subjects under fasting conditions, with meals, and after meals showed that the resulting alcohol curves in the blood are different, the highest level being reached in the fasting state. In experiments in which olive oil or paraffin oil was given to volunteers simultaneously with the ingestion of alcohol, there was a decrease at 1/2 hour of 17% of the average blood concentration in the group drinking olive oil, as compared with the control or those having ingested paraffin oil. After three hours the average blood alcohol concentration was 16% higher with olive oil and 8% higher with paraffin oil. The ingestion of these substances may delay the symptoms of intoxication but do not diminish them, if the blood level is high enough.

Observations relative to the action of glycocoll on the blood level obtained with the simultaneous administration of alcohol show that there is no alteration, combination or destruction of alcohol by any action of the glycocoll, but that alteration in the curve may occur, due to prolonged retention of alcohol in the stomach and correspondingly retarded absorption.

When diluted to a constant concentration of 13% alcohol by volume, the absorption rates of alcohol, Scotch, bourbon, gin, port and burgundy differ, as reflected by the time required to reach maximum level in the blood. This may be due to the presence of different buffering substances in the beverage. When port wine is buffered to the same pH and acidity as alcohol, there is an identical rate of absorption.

Serianni (18) in a study of blood alcohol concentrations resulting from wine drinking according to dietary habits of Italians, noted that when wine is taken with the meal the peak blood alcohol concentration is reached appreciably sooner than when wine is taken on a fasting stomach. When wine is taken in the fasting state, the peak blood alcohol level is approximately twice the level obtained when the alcohol or wine is given during the meal; the effect of a meal on the blood alcohol concentration lasts for four hours.

Fasted dogs receiving five diluted beverages (alcohol, canna, grappa, cognac and whiskey) on different occasions are reported to have all showed similar blood alcohol curves independent of the beverage used or the dilution which it is administered.

The rate of absorption of alcohol in man is generally less following the drinking of beer as compared with the ingestion of a strong liquor. The maximum blood level at low doses can be decreased by nearly 50%.

The presence of disease states may influence the rate at which alcohol is absorbed, thus influencing the resulting blood alcohol levels. Persons suffering from achlorhydria or gastritis will have different rates from normal persons. A study of alcohol distribution in 40 cachexic patients with severe metabolic disturbances of a lipophilic dystrophy type indicates that maximum levels occur much sooner than in normal subjects. The rates of metabolism are also more rapid. The results of these investigations should be kept in mind when predicting former blood levels from a single analysis.

In an evaluation of effects of malnutrition on rate of oxidation of alcohol, returned prisoners of war with both dry and wet dystrophy received, while fasting, a beverage consisting of a 33% alcohol solution. Absorption was delayed and a series of peaks appeared in the curve. Irregularities are explainable by diffusion of alcohol into the edema fluid or into pathologically changed tissues in general, perhaps due to changed permeability of capillaries. Oxidation proceeded at a normal rate but the blood alcohol values were so irregular that conclusions for forensic purposes could not be drawn and extrapolation could not be made with respect to blood alcohol concentrations in the path or the amount of alcohol ingested. Absorption of alcohol into the blood was delayed in many cases.

The speed with which certain amounts of alcohol are drunk determines in part the shape of the alcohol curve. This has forensic significance as regards the possible maximum concentration reached and its duration.

It is generally accepted that sympathomimetic drugs given peritoneally or orally delay absorption of alcohol from the alimentary tract and postpone intoxication; that parasympathomimetic drugs tend to enhance the absorption of alcohol from the alimentary tract. A series of tests of substances influencing the sympathetic and parasympathetic nervous system, reserpine (a central sympathetic inhibitor), atropine (a peripheral parasympathetic inhibitor), and hexamethonium (a ganglionic blocker) produced no effect on the absorption rate. Chlorpromazine elevated the blood alcohol level above that expected, but did not do so for other substances absorbed in a manner similar to ethanol. Elevation of the blood alcohol level in rabbits and man taking this drug is interpreted as being due to an inhibition of metabolism of the substance, not to the rate of absorption. Among other things, change in the sympathetic tone incidental to emotional states

may influence the gastric motility, and thus the rate of absorption of alcohol. Psychological factors leading to distaste cause a slower absorption with a higher and later maximum blood alcohol level. Warm beverages are absorbed more rapidly than cold. Performance of tasks of concentration may result in lower levels of blood alcohol. Cortisone, simulating stress situation, has no apparent effect on blood alcohol concentrations.

Delaunois (19) reports an increased rate of absorption of alcohol given intragastrically to dogs following application of either external or internal heat.

Summarizing these effects, it may be concluded that as absorption through the stomach wall represents only a small percentage of the total intake of alcohol, it is evident that anything which increases gastric motility and stomach emptying time and the passage of alcohol into the intestine will have a marked effect on alcohol absorption.

Absorption from the Bladder

In studies evaluating the ante mortem diffusion of alcohol through the mucosa of the bladder, it appears that the equilibrium between the blood and urine alcohol concentrations may be established by direct passage of alcohol through the mucosa of the bladder, that alcohol passes through the mucosa of the bladder more readily from the blood to the urine than from the urine to the blood, and that alcohol may be lost from the urine through the mucosa of the bladder if the concentration in the bladder is disproportionately greater than in the blood. In the postmortem event, diffusion of alcohol through the mucosa of the bladder can also occur, but only when there is a great disproportion between the alcohol concentration in the blood and urine.

Absorption from the Skin

Absorption of alcohol through intact human skin is generally considered to be negligible. In experimental situations in which subjects have been treated with external applications of 95% solution for nine hours, no detectable blood levels have been achieved, when care has been taken to avoid inhalation. However, when a tincture of iodine is applied to shaved, wounded and treated skin of animals, a blood alcohol level of as great as .06% may result, indicating percutaneous absorption may be brought about by this procedure, and that alcohol can reach measurable levels in the blood following medical manipulations of this type.

Absorption from the Respiratory Tract

Alcohol vapors can be absorbed through the respiratory tract, and fatal intoxications occasionally occur. Severe alcohol intoxication observed in children whose extremities had been maintained in orthopedic preparation containing 95% alcohol, is due to inhalation of vapors, as indicated by the absence of any significant quantities of alcohol in volunteers who were not allowed to inhale the vapors. When subjects breathe air containing alcohol in a closed system, 62% of the alcohol in the inspired air will be absorbed, irrespective of the concentration or the rate of ventilation. MacLeod (20) found that the mean intoxication threshold of ethyl alcohol vapors in the air is 0.20% as measured by a failure of rats to pass a designated coordination test. Administration of dexedrine did not alter this threshold, but a raising of the threshold could be accomplished by gradual increase of the air alcohol concentration.

Treon (21) reports narcosis to occur at concentrations of 0.64% after 12 hours exposure, while death is reported at 1.27% for 21 hours exposure. In breweries the concentration of alcohol in the air varies between 0.004 and 0.075%, while in taverns with poor ventilation the level does not exceed 0.06%. These concentrations could not provoke a positive alcohol reaction in normal individuals; however, in individuals treated with tetraethylkiuram disulfide (TETD), a level above 0.10% is probably unsafe.

Absorption by Other Routes

Alcohol injected intrathecally in spinal paraplegics results in detectable levels in the blood within 5 to 15 minutes when alcohol is placed not higher than the 10th thoracic vertebra.

Distribution

Once alcohol is absorbed within the body, it is distributed throughout the organs and tissues in proportion to the fluid content. It appears both extra- and intracellularly. The partition ratio between air and the body fluids is vastly in favor of the latter. As determined by Harger (22) the partition ratio of alcohol between air and blood ranges with temperatures from .035 to .562; that between air and water from .092 to .703; and that between air and urine between .080 and .590. Alcohol distribution in the tissues of rats 30 minutes after oral administration gives the following values for the different tissues, expressed in terms of the blood as 100: Liver 68.7, heart 41.8, brain 21.1, spleen 71.6, kidney 65.2, pancreas 41.0, muscle 37.0, bone 18.8, gonads 46.9, and lungs 58.2.

Equilibrium between the blood and all tissues in the body as estimated from the shape of the blood alcohol curve, occurs approximately 60 minutes following intravenous administration, regardless of the rate. Following equilibration, muscle contains 80% of the alcohol present in the plasma, and the fat only 20%. Alcohol determined in various fractions of blood after centrifuging shows uniform distribution between the erythrocytes and plasma within 15 minutes after ingestion. Up to 70 minutes following absorption, the alcohol level of capillary blood averages 7.5% above that of venous blood, and may be as much as 15 to 22% higher.

The ratio of the concentration of alcohol in serum to that of whole blood may vary in the same person. However, in vitro the ratios are constant following the hematocrit values. The alcohol concentration therefore follows the water content of the tissues, a point which is of considerable significance when dealing with cadaver blood. Determination should be made on total blood, rather than serum or plasma. The ratios of saphenous to heart blood 60 minutes after ingestion of alcohol in amounts of 1 to 4 gm/kg body weight, averaged .99, and the femoral to heart blood ratios at 30 minutes averaged .89. This data indicates that there is no great lag in the alcohol level in the peripheral venous blood as compared with arterial blood.

Since the concentration in the brain is of importance in medicolegal cases, the question of the distribution between this tissue and body fluids used for analysis becomes important. The level of alcohol in the brain, peripheral blood and heart blood 10 minutes after oral administration shows different blood-brain ratios, being relatively .88 for saphenous, 1.24 for heart, and 1.19 for brain blood. Since blood for intoxication tests is usually taken from a peripheral vein, samples drawn soon after drinking may yield low values for estimated brain alcohol. Ratios of alcohol concentration in the cardiac blood to brain blood in a series of coroner's cases vary from .88:1 to 1.52:1. This is interpreted as representing various states of absorption. In a series of police-suspect drunken driving cases, alcohol concentrations determined simultaneously in the urine and blood show a ratio of 1.21:1 with a range of .69:1 to 1.71:1. Spinal fluid and jugular blood both closely follow brain alcohol levels. Since these specimens are impractical to obtain in living men, saliva alcohol levels have been recommended by some in evaluation of brain levels, since they follow the latter closely.

Analysis of different portions of the brain of mice administered alcohol in doses of 3 gm/kg and sacrificed at varying periods up to 3 hours thereafter, show a blood brain alcohol content for the telencephalon of 1.45; the diencephalon 1.83; the mesencephalon 1.83; the cerebellum 1.81; and the medulla oblongata 2.35. It may be concluded that the variation in the alcohol concentration depends upon the blood supply rather than the water content, based on water analysis of the cerebral tissue.

Duration of anesthesia produced by alcohol in normal rabbits has been found by Susumu (23) to be directly proportional to the concentration in the brain, and inversely proportional to the concentration in muscles. In the alcohol-habituated rabbit there is a shortening of anesthesia, a decrease of alcohol concentration in the brain, and an increase in concentration in the muscles. The ratio of alcohol concentrations in other tissues, including the kidney, liver, lungs and fat, is not influenced by alcohol habituation.

Purposefully induced emesis and blood-letting is reported to increase the blood alcohol level by .01 to .03%, Partial exsanguination produces irregularity in the blood alcohol curve in rabbits, and it is interpreted by some, though not necessarily correctly, that this procedure causes a loss of oxidative processes. In contrast to these results, experiments conducted in man to evaluate the effect of whole acute blood loss on the alcohol level indicate that loss of from 4.5 to 8.7% of the total blood volume (up to 500 ml) has no significant influence on the rate of distribution or elimination and should not be considered as an influencing factor in the forensic interpretation of blood alcohol tests.

In a study of the effect of shift of body water and blood on the blood alcohol curve, a decrease in the amount of circulating blood results in a steeper decline in the blood alcohol curve, and conversely, an increase in the amount of circulating blood causes the blood alcohol curve to flatten out. From this it has been concluded that short segments of the curve are not indicative of the rate of metabolism of alcohol and that interpretation and extrapolation from the blood alcohol findings must be done with caution.

Gruner (24) reports an alteration in disappearance rates of alcohol from subjects during a period of no movement in comparison with periods of violent exercise, which he relates to a shift in the amounts of blood and water in the orthostatic position. A decrease in the amount of circulating blood is followed by an increase of alcohol in tissue water. Since similar conditions occur in a state of collapse, fluctuation of the blood alcohol curve may be expected in persons in shock.

Determination of the concentration of alcohol in various organs and fluids of human cadavers indicates that the concentration is inversely proportional to the fat content and directly proportional to the water content and vascularity of the tissue, with the notable exception of the liver. The content of bone marrow and subcutaneous fat is very low, even in cases of fatal alcohol intoxication. Prag (125) reports blood-brain alcohol ratios in 10 cadavers as varying between 1 and 1.31 when death occurred less than 12 hours before the test. Diffusion of alcohol in various concentrations from isolated stomachs submerged in water or saline solutions indicates that the usual diffusion laws apply to stomach wall for at least 40 hours

after death. The quantity diffusing in 40 hours amounts to between 49 and 100%, from an 8% solution, and between 17 and 63% with a 33% concentration. The significance of this finding relates to the possibility of alcohol diffusing into the stomach wall to the heart post-mortem.

The diffusion of ethyl alcohol in human cadavers has been demonstrated by a number of investigators, including Huber (26), based on samples taken from various portions of the body 24 to 72 hours after the original determination. While blood alcohol concentrations may not change, they may be altered from .22 to .48%. Administration of 300 cc of 33% alcohol into the stomach of six human cadavers during a period of 12 to 40 hours after death, results with time in a diffusion of alcohol into the heart blood, while blood from the lower extremity remains unchanged. In another experiment, when 100 cc of 15% alcohol was placed between the stomach and the diaphragm of cadavers, an increase in alcohol concentration registered in the heart blood in one-third of the cases. An increase in the alcohol concentration in the pericardial fluid up to .3% was found in two-thirds of the cases.

In a series of examinations made at the San Francisco Coroner's office, blood samples obtained on autopsy from the heart and femoral vein showed differences in approximately 10% of cases, ranging between .03 and .09%. The variation is dependent on the time lapse between drinking and death, and death and autopsy. Based on the above, it is highly desirable that alcohol values should not be determined, for forensic purposes, from the heart blood of cadavers if there is any alcohol left in the stomach after death. Alcohol passes more rapidly into the aqueous humor of the eye than any other body fluids.

The alcohol content of chyle may be much less, equal to, or greater than that in blood, depending upon the fat content of the chyle and the time after ingestion. In general the concentration of alcohol in the bile is reported as reaching higher levels than that in the blood, though reaching this level at a later time and remaining elevated longer. Further, patients with liver cirrhosis and infectious hepatitis are reported to have lower alcohol bile levels than the normal subjects. Alcohol injected directly into peritoneal fluid of patients with ascites gives a high ascitic fluid alcohol curve immediately, which falls precipitously while the blood alcohol curve remains low and horizontal.

Excretion

Excretion is relatively unimportant in terms of the total quantity of alcohol which disappears from the body. The amount is generally about 2% and rarely exceeds 10% of the total quantity absorbed. While alcohol is

found in the tears, saliva, feces and perspiration, the body excreta containing the major quantity are breath and urine. The breath rarely contains more than 2 mg of alcohol per liter, and while hyperventilation results in a marked increase in the percent of alcohol leaving by this route, in comparison with normal, the total quantity in the breath is small in comparison with the quantity metabolized per unit time. The quantity excreted in the urine is similarly small. The urinary level reflects the blood level and in moderate drinking does not exceed 0.2%. While increased elimination of alcohol by massive intravenous infusions of physiological salt solution has been reported as successful in the treatment of acute alcohol poisoning in dogs, the procedure is with little merit in the treatment of human acute intoxication. We must conclude that because of the small quantity of alcohol excreted by any route, any therapeutic attempt aimed at increasing the elimination of alcohol is of little or no effect. After large doses, rabbits excrete ethanol as a glucuronide, the amount of conjugation rising with the increasing dose. The compound is excreted only for the day following dosing.

Metabolism

The metabolism of ethyl alcohol has been the subject of many studies, not the least of which has concerned the question of the formation and tissue levels of endogenous alcohol. McManus (27) found between 23 and 145 μg of ethyl alcohol per 100 gm of liver, kidney, heart and skeletal muscle obtained from rats and from rabbit liver. He established the identity of ethanol by excluding other possible reactive substrates and determined the quantity of acetaldehyde which might be expected to be formed. The contribution of intestinal bacterial to the production of endogenous ethyl alcohol was eliminated through feeding rats a diet supplemented with bactericidal agents and comparing the liver alcohol found in this group with that of animals fed an ordinary diet. In a further study of its origin, labeled ethanol was obtained from labeled pyruvate incubated with liver slices under anaerobic conditions. Hecksteden (28) reports that the "normal" alcohol content of the blood of subjects before and after exercise was less than .007%. Endogenous alcohol in horse muscle was found to be .0048%. This is increased by autolysis at 38° to a maximum of .03%.

Though there is considerable disagreement in the literature regarding the occurrence of endogenous ethanol, there is no disagreement as to the relative unimportance of this particular contribution to the economy of the body, since all assumed it must be trivial. Most chemical tests for blood alcohol at this level are inadequate, and the finding of presumably endogenously formed ethanol is generally an artifact. It has been concluded by

Lester (29) in a review of the literature, that ethanol as such, and not another volatile reducing substance, does occur in human beings and other mammals, and that it is formed endogenously and not as a result of bacterial fermentation in the intestinal tract. The concentration may vary with the individual and it may be increased in a number of ways, notably by hypoxia associated with high altitudes or in decompression chambers by decreased partial oxygen pressure.

While previous levels of endogenous ethanol have been stated as lying between 20 and 30 mg/liter of blood or serum, recent determinations made by gas-liquid chromatography indicate a maximum of 1.5 mg/liter as determined by analysis of alveolar air. Direct determination of the concentration of ethyl alcohol in rat liver by gas-liquid chromatography gives a value of 9 mg/kg in contradistinction to one-tenth these values when intraperitoneally equilibrated nitrogen is used in the living animal. It is suggested that this formation of alcohol may take place during handling of tissues. The possible role of endogenous ethyl alcohol in the theory of the etiology of alcoholism appears to be excluded by identification of these minute quantities.

The route of metabolism of most primary alcohols follows oxidation of the OH group to an acid. In 1943 Dewan (30) demonstrated that the brain contained an alcohol oxidation system, and that acetaldehyde and acetic acid were products of this oxidation in vitro. Liver has a similar system and both require nicotinic acid and riboflavin. The liver is evidently the main site of primary oxidation, but the central nervous system is capable of performing the function to a lesser degree.

Bartlett (31) made the following observations as regards the metabolism of alcohol using radioactive alcohol. Rapid conversion to CO_2 occurs with peak activity from 1 to 5 hours after ingestion; 90% of the alcohol is accounted for as CO_2 within 10 hours after ingestion of even large quantities. No difference is noted in the rate of oxidation between control and habituated animals. Others using C^{14}-tagged alcohol also demonstrated that alcohol commences to be metabolized in vivo immediately, without any latent period, and subsequent plateau formation indicates an equilibrium between the speed of formation and elimination of CO_2.

Serial alcohol and acetaldehyde concentrations measured during a period of 10 hours showed molar ratios of the two substances at a maximum discrepancy to be approximately 104:1 one hour after ingestion, and to decline to 15:1 as alcohol levels fell. Acetaldehyde appears to have no effect in itself on the rate of metabolism of alcohol.

Using heavy hydrogen as an index and the in vivo acetylation of sulfonamide drugs, Bernhard (32) demonstrated the formation of acetic acid as an intermediate production in catabolism of ethyl alcohol.

Incorporation of tagged ethanol into glycerol and glycogen was demonstrated by Schiller (33). The glycerol was found to be labeled on a terminal carbon by ethanol which was tagged on the 1-carbon and on the middle, as well as end carbons by ethanol tagged on the 2-carbon. Glucose and glycogen were both more heavily labeled on carbons 1, 2, 5 and 6 than on 3 or 4. These data support the postulation that glycerol and glycogen are labeled following incorporation of ethanol in the TCA cycle, with decarboxylation of oxalacetate to pyruvate, a reversal of glycolysis.

A number of excellent reviews have appeared on the subject of the rate of metabolism, including that of Newman (34) in 1947. Different species metabolize alcohol at different rates, the cat doing so more rapidly than the rat, which is faster than the dog. The rate in mg/kg/hr for the rat is 270 mg as determined by changes in blood concentration, and 293 mg as measured by analysis of the carcass after a given elapsed time. Using tagged alcohol, no difference in metabolism rates was demonstrated in animals habituated to 10% alcohol and non-habituated animals. Rates obtained indicated that 14.7% of the dose disappeared per hour with a mean utilization rate of 294 mg/kg/hr. Based on cumulative CO_2 recoveries, however, the rate becomes significantly lower in animals previously treated with alcohol, and it has been concluded that some alcohol is utilized by other than main oxidative pathways in the habituated animal.

Considerable differences of opinion exist as to the effect that the tissue concentration exerts on the rate of disappearance. Marshall (35) was not able to obtain a constant rate of disappearance of alcohol from dogs administered between .5 and 1 gm/kg of body weight orally. The alcohol plasma concentration varied greatly from dog to dog as well as in the same dog at different times, with a maximum utilization rate of .30% per hour which later fell to .17% per hour. At high levels the rates of disappearance were rather more consistent. At low concentrations, however, as with other drugs, the rate of disappearance from the plasma becomes proportional to the amount present. Nelson (36) utilizing constant injection of alcohol in dogs, concluded that the rate of alcohol metabolism is not conditioned by an initial concentration of hepatic alcohol, and no relationship could be found between rate of metabolism and rate of injection. There was, however, a mean daily variation in the same animal which approached 40%, the reason for which was not discovered. Eggleton (37) states that the metabolic rate of alcohol is directly dependent upon the concentration in the body and is raised about 30% for every 100 mg% increase in plasma alcohol concentration. Cutting (38) has held that there is a definite relationship between dose

and the rate of ethyl alcohol metabolism, a 40% increase in the latter resulting from an increase in blood alcohol concentrations of .15%.

When mice are given exceptionally high doses of alcohol, the rate of metabolism as determined by the quantity in their blood and in their whole body seems to be greater at one-half hour than at three hours. This effect is true whether the alcohol is given by mouth or vein, or whether the animals were fasted. When lower doses are given, the metabolism rate is essentially indistinguishable with time. Based on this work the inference has been made that the normally constant oxidation rate in this species may be influenced by certain circumstances relating to the high concentration of alcohol reaching the liver, and that estimated maximal rates of oxidation are low.

Utilizing an alcohol dose range in vivo in rabbits of from .064 gm/kg to 4.5 gm/kg, there occurs an increase in the rate of oxidation per kg per hour up to 2 gm, after which the rate levels off from 2.5 to 3 and starts on the decline. In animals starved between 24 and 120 hours, the peak is reached at 1.5 to 2 gm, but the decline starts at 2 gm/kg. It has been suggested that the effect of fasting is due to loss of liver enzymes necessary for alcohol oxidation. It would seem, however, that even with the concentration of alcohol used and with a possible 30 to 40 % reduction in alcohol dehydrogenase, there would still be ample enzymes to maintain the rate.

The rate of metabolism of alcohol by mice at the end of one hour is 625 ± 160 mg/kg/hr, and at the end of three hours is 598 ± 91 mg/kg. The rate appears to be linear during this time.

Most of the disagreement of linearity of rate revolves about low levels in the blood. Loomis (39) established through a constant infusion technique, that in dogs primed with alcohol to give levels of .02 to .04%, 3 mg/kg per minute are required to maintain the blood alcohol level at the priming dose figure, irrespective of the blood level. Allowing for the many variations in experimental design, it appears that the rate of utilization does not depend on the concentration and is essentially linear, but that it may vary from individual to individual and from species to species.

In an effort to clarify the effect of habituation, Newman (40) allowed dogs access to 10% alcohol as the only source of fluid. These dogs consumed 5.52 gm of absolute alcohol per kg of body weight per day, and thus metabolized alcohol at the rate of 230 mg/kg/hr. When additional alcohol was infused intravenously at a constant rate, the metabolic utilization increased by a factor of 30 mg/kg/hr in excess of the maintenance dose. Newman concluded from this work that the maximum daily consumption of alcohol by a man of average weight is represented by a quart of 100 proof

liquor, that estimates greater than this are in error, and that this consumption can be achieved only by maintaining the blood alcohol concentration at a high level.

Other investigators utilizing a self-selection procedure in which groups of rats were divided into high and low consumers of alcohol depending on their average daily intake, and subsequently challenging the animals with radioactive tagged alcohol at doses of 0.5 to 3 gm/kg, could not detect any differences in the rate of oxidation of drinkers and non-drinkers, or between different strains. The maximal oxidation rate was 300 to 400 mg/kg of body weight per hour, and occurred at levels of ingestion of from 2 to 2.5 gm/kg of body weight. The rats voluntarily selecting the alcohol were consuming up to 4 gm of alcohol per kg per day. Total alcohol consumption, particularly in those consuming large amounts, approximated the maximum capacity of the animal to oxidize alcohol during the entire day. A change in rate of alcohol oxidation with change in blood concentration was not demonstrated even at this high level of alcohol dosage.

In man the average utilization rate is equivalent to a drop in the blood level of 0.018% per hour. Variations occur within the range of 0.01 to 0.025% per hour. The rate of disappearance at very low alcohol levels is of the order of .01%.

In limited studies Wilson (41) notes a difference in the rate of metabolism of alcohol at different times of the day. These variations were related in part to diurnal body temperatures, principally to food intake, but not to sleep itself. He concluded that the time of day may be important in the study of the metabolism of alcohol or its effects.

The effects of various disease states, chiefly those involving the liver, have been studied as regards the utilization of alcohol. Only 1 of 10 alcoholic patients with cirrhosis of the liver showed an abnormal alcohol curve following ingestion of 0.6 cc of alcohol per kg of body weight. The alcohol curve in the ascitic fluid rose slowly, crossed the alcohol curve after two hours, and remained above it thereafter. Diabetic patients administered ethyl alcohol alone or with sodium acetate by intravenous injection at a constant rate did not differ in respect to the quantity of alcohol excreted in the urine or as regards the rate of alcohol utilization, whether patients were controlled by insulin or not. Neither did this group differ in utilization rate when compared with a group of normal subjects. Blood alcohol concentrations in healthy subjects and in patients with various diseases after the administration of alcohol, indicated no essential difference in rate of disappearance in the presence of thyroid disease, diabetes, anemia or hepatitis. In contrast to these findings, Bernstein (42) measuring alcohol utilization in healthy patients, those with mild and those with rare acute

liver disease, found the mean rate to be 107, 102 and 91 mg/kg/hr. respectively. In healthy subjects the administration of fructose increased the metabolism rate by 24%, but in subjects with severe hepatitis by only 9%.

Experimentally a marked decrease in the rate of disappearance of alcohol from the blood of rats with obstructive jaundice produced by common bioduct ligation was observed as early as 24 hours after jaundice had set in. Destruction of the central part of liver lobule of rats by the administration of carbon tetrachloride does not seem to have any influence on the rate of oxidation of ethyl alcohol in vivo. A select necrosis of the most peripheral parts of the liver lobule as produced by phosphorous, decreases the rate of alcohol metabolism to about half of that prevailing in the intact rat. This clearly suggests that the peripheral portion of the liver lobule participates more actively in the oxidation of alcohol than does the central portion.

The effects of various physical factors on metabolism rate of alcohol have been observed. Mosinger (43) determined the rate of oxidation of alcohol directly through successive blood alcohol determinations and indirectly by measurement of oxygen in output of respiratory quotient. He concluded that alcohol disappeared from the blood 50% faster in persons working at 38° C than at 21° C. These results are generally in conflict with information obtained by other experimentalists, who report no significant effects due to temperature. Persons administered alcohol and subjected to moderate to strenuous exercise showed an hourly utilization rate of 0.019% in comparison with their control value of 0.013%. The conclusion relative to this study was that physical work accelerates the metabolism of alcohol, providing the work is of considerable duration, though loss through perspiration and the breath may contribute also.

It has also been observed that the rate at which alcohol disappears from the blood may be lower in persons living in a cold climate, and is less among undernourished persons at work.

Whole body irradiation of 1500R did not alter the metabolism rate of ethanol in mice. The rate of disappearance of alcohol from the blood stream is not altered following experimentally administered trauma to the cranial vault. Newman's (44) observations on human subjects who were given alcohol and then convulsed by 60 cycle alternating current revealed no evidence of metabolic acceleration, and it may be concluded that electrically induced convulsions are not effective in significantly influencing the rate of alcohol metabolism in man.

Elevation of body temperature produced by diathermy does not significantly alter the oxidation rate of alcohol administered to dogs. On the other

hand, dinitrophenol in doses unsafe for human use moderately increased the loss of alcohol from the blood, independently of the final body temperature.

A number of chemical agents, some unrelated to many associated with the normal biochemistry of the body, have been examined with regard to their influence on metabolic utilization of alcohol. The drugs acetophenetidin, acetanilid, aminopyrine, aniline, and para-aminophenol were administered to rats in doses of 200 to 800 mg/kg in order to determine whether there was any tendency to delay the oxidation of ethyl alcohol. Only acetophenetidin had any effect. The rate was depressed, but significantly so only in doses of 400 mg and above, and provided it was given at least one hour before the alcohol. If given 18 hours before, the effect was less consistent or no effect was observed.

Pentobarbital decreases the rate of utilization of alcohol in dogs intravenously administered a dose of 1 gm/kg as a 10% solution. The reduction average is between 4 and 18% and cannot be attributed to the decrease in body temperature or the decrease in elimination of alcohol through the lungs and kidneys. It also affects the hour to hour, but not the day to day, variability in the rate of alcohol utilization.

Amphenone, an agent which profoundly affects metabolism and particularly the activity of the adrenal glands, results in an increase in adrenal weights and the total quantity of adrenal cholesterol and prevents the usual reduction in cholesterol content after challenge with alcohol. Amphenone feeding does not influence either the severity or duration of alcohol intoxication, or the rate at which alcohol is reduced in the blood.

Daily oral administration of carbutamides for periods up to two weeks has no effect on the rate of disappearance of alcohol from the blood of dogs, nor does it increase blood acetaldehyde after test doses of alcohol. Administration of chlorpromazine, promethazine and pethidine intraperitoneally does not influence absorption of alcohol from the gastrointestinal tracts of rabbits, but it does delay oxidation of alcohol over a period of three hours. There is potentiation of the effect by cold. Chloroprophenpyridamine, probanthine and Dormison have no effect on the rate of alcohol metabolism in rabbits.

In experiments during which dogs receive acetaldehyde intravenously or accumulate higher levels by TETD administration, no increases are noted in the rate of metabolism of alcohol. In some cases these procedures may retard it slightly.

3-Amino-1, 2, 4-triazole, which is effective in reducing hepatic catalase activity *in vivo* as well as *in vitro* in dogs, rats and mice, has nc effect on the rate of ethanol metabolism. It may be concluded that hepatic catalase does not play an important role in ethanol metabolism in these species.

A number of agents have been advertised as capable of exerting a sobering-up effect on intoxication by lowering the blood alcohol. One of these called "Contra" or "Stop" was tested in a number of subjects and the rate of elimination was found to vary between the normal range of .011 and .024%; it is concluded that this drug could have no effect.

Delaunois (19) demonstrated an increased utilization of alcohol in dogs administered 7 mg/kg of dinitrocresol, but not 3 mg/kg, while external heat had no effect on the rate of elimination. Fasted male dogs receiving alcohol intravenously and tri-iodothyronine in amounts of .33 mg/kg had no significant difference in the rate of decline of alcohol from the blood than control animals. Assays for liver alcohol dehydrogenase activity revealed no increase when tri-iodothyronine was added to the homogenate. However, there are clinical reports to the effect that l-tri-iodothyronine administered intravenously may produce a significant increase in alcohol metabolism in man. The studies await confirmation.

There are considerable variations as to points of view regarding the effects of insulin and carbohydrate metabolism on the disappearance of alcohol from the blood. Clark (45) demonstrated that the rate of oxidation of alcohol in animals is a constant and linear function of time, and that glucose alone has little effect on the disappearance in well-fed animals. The injection of insulin does increase the rate of alcohol oxidation during the subsequent two hours, and various manipulations relative to the pancreas and liver can reduce the rate of alcohol oxidation. Insulin injections can return the rate to normal in pancreatectomized but not hepatectomized animals. Johannsmeier (46) was unable to demonstrate any increase in the rate of alcohol utilization in sheep by the administration of fructose, glucose, pyruvate or diphosphopyridine nucleotide. Neither was the rate of utilization increased in four human subjects given fructose. Pyruvate values were increased by both fructose and glucose administration, but much greater increase occurred after physical exercise, and on the basis of enzyme kinetics he has postulated that fructose could not possibly elevate the oxidation rate of ethanol.

When experimental situations are invoked where rats are given progressively decreasing quantities of food, the metabolism of alcohol will stabilize at about 75% of the original quantity. This occurs after 50 days. When thiamine-deficient diets are offered, the weight of the animals does not stabilize and the amount of alcohol metabolized during the specific time

period of six hours continually decreases until death. The limitation in alcohol oxidation may be related to both liver size and enzyme concentration in the liver.

There are a few possible mechanisms whereby carbohydrates can speed the rate of elimination of alcohol. These are the decrease of the dissociation constants of the ADH-DPNH complex, an increase of DPN concentration which results in the increase in the steady state concentration of the ADH-DPNH complex, and oxidation of the ADH-DPNH complex by means of an aldehyde that reacts with ADH. The average rate of alcohol elimination is increased by 6% after glucose and 34% after fructose. With the latter sugar, the third mechanism above may be responsible, since liver ADH catalyzes the reduction of glycerylaldehyde to glycerol.

Gregory (47, 48) and others were unable to confirm these observations and found that alcohol curves in dogs showed no influence of pyruvate. Further experiments by this group indicated that insulin, glucose or insulin plus glucose did not increase the rate of metabolism of ethyl alcohol experimentally in dogs. The question is raised whether the increased rate of disappearance of ethyl alcohol from the blood of intoxicated men may not be due to a non-specific effect of treatment with fluids.

Hulpieu (49) also re-investigated the possible role of pyruvate on alcohol metabolism. He concluded that administration of pyruvate did not alter the rate of decline of alcohol from the blood, regardless of the route of administration or of the fasting state of the animal. Further, sodium arsenite, an inhibitor of the pyruvate oxidase system, had of itself no effect on alcohol metabolism in vivo, as indicated by blood alcohol curves in animals. Fluctuations in the rate of disappearance from the blood may represent variations in local blood supply rather than differences in oxidation rates. At low levels of alcohol infusion Stuhlfauth (50) reports that levulose does affect metabolic rate, but the following substances have no effect: ascorbic, pyruvic, glutaric, and oxalacetic acids, lactoflavin, adenotriphosphate, cytochrome, diphosphopyridine nucleotide, vitamin B_{12} or pantothenic acid.

Metabolism rates varying between 271 and 512 mg/kg/hr were reported in normal rats when maintained on protein-free diets; there was a decline in rate to approximately one-half, while animals fasted for 48 hours showed a mean rate of disappearance of .017% from the blood stream, a value of approximately one-third that in the normal rat. Administration of diphosphopyridine nucleotide and sodium pyruvate in amounts of 20 mM/kg increased the utilization rate, but a similar increase was noted after injection of saline. Hypophysectomy and adrenalectomy increased metabolic rates inconstantly. The rate of oxidation between doses of 1 and 2.5 gm/kg

is fairly constant and the amount of alcohol dehydrogenase is not the sole limiting factor in the rate of oxidation. The rate of alcohol disappearance from the blood stream of normal dogs is .02% per hour. This rate is unaffected by oxygen, carbon dioxide or added pyruvate as indicated by Kinard (51).

The ultimate metabolism of alcohol into carbon dioxide is reported as inhibited by administration of pyruvate or acetate to rats. Thiamine deficiency also decreases the rate of utilization by approximately 16%. Pretreatment with niacinamide prevents the inhibition by pyruvate and acetate. Correlating these findings with other observations relative to the reported decrease in alcohol metabolism by human subjects given sugar and alcohol, in comparison with alcohol alone, it is concluded that the effects of pyruvate, acetate and glucose represent a competition for DPN, since this coenzyme is also required for oxidation in the tricarboxylic acid cycle.

Normal rats administered 20 mM pyruvate of acetate have a decreased rate of alcohol oxidation as indicated by radioactive CO_2 formation, indicating that inhibition is at the first stage of oxidation to acetaldehyde. Also, the disappearance of alcohol from the blood is delayed, indicating that the inhibition is at the first stage of oxidation to acetaldehyde. Large amounts of niacin given prior to the pyruvate prevent the inhibitory effects of that substance. The inhibition of pyruvate is decreased in the presence of thiamine deficiency, which suggests that the inhibition is due to competition for the coenzyme DPN, that the coenzyme preferentially reacts with TCA-cycle intermediates rather than alcohol oxidation products when the DPN is available in limited amounts.

Whittlesey (52) reports that pyruvate in the quantities of 1.25 or 2.5 mM/kg does not affect the rate of alcohol metabolism while 5 mM increases it approximately 18 to 22%, whether animals were pretreated with pentobarbital or were not anesthetized. Alanine given in equal molar doses affects the rate of alcohol metabolism similarly.

Early experiments by Westerfield (53) indicated that in dogs there was an increased disappearance of alcohol from the blood in the presence of pyruvate, but that excessive pyruvate did not increase the disappearance beyond a maximum rate of about .02% per hour. He equated variations in disappearance from the blood with the pyruvate supply. Likewise dl-alanine produced an increase in the rate of alcohol metabolism which was equated to conversion of this substance to pyruvate. The theory was then proposed that the acetaldehyde resulting from alcohol oxidation undergoes condensation with pyruvate to form acetonin. Later Westerfeld (54) while studying the coupled oxidation-reduction of alcohol and pyruvate *in vivo*, determined that following administration of pyruvate during alcohol

metabolism there occurs an alteration in the metabolism relationship normally existing between pyruvate-lactate and alcohol-acetaldehyde. The lactate and acetaldehyde are relatively increased at the expense of alcohol and pyruvate. He concluded that dogs are able to metabolize acetaldehyde much more rapidly than it is being formed from alcohol, and that the slowest reaction in alcohol metabolism therefore must be the oxidation of alcohol itself to acetaldehyde. The pyruvate effect is due to increasing the rate of this oxidation. He also demonstrated that the rate of disappearance of acetaldehyde from blood is not appreciably different, whether or not alcohol was being metabolized at the time of its administration. Lactate subsequently administered did not increase the rate of alcohol metabolism appreciably. Other carbohydrate intermediates and hormones affecting their metabolism have been the subject of much research. Loomis (39) demonstrated that administration of sugar with or without insulin has no effect on the metabolism rate, nor does pre-treatment with TETD.

The rate of disappearance of alcohol from the blood of 21 alcoholic patients prior to treatment with insulin, glucose and "bettalin" was compared to the rate after treatment. An increase of 9.9% was reported during treatment calculated on the basis of the percent of alcohol present. This seems to be of questionable significance. Klein (55) reports that fructose ingested simultaneously with alcohol causes a marked increase in the oxidation rate of the latter; other sugars or foods did not cause the same effect.

In counterdistinction to the experience of most investigators, Dontcheff (56) developed data which indicated that in rats the type of diet affects the rate of oxidation of alcohol. Carbohydrate diets tend to increase, and fatty diets decrease this rate. Insulin, adrenalin and thyroid affect the oxidation rate in different directions. Clark and Hulpieu (57), following the rate of disappearance of alcohol from the blood stream of dogs, interpret their results as indicating that infusion of fructose definitely increases alcohol disappearance rate, that intravenous insulin results in an equivocal increase, and that dextrose, pyruvic acid and insulin plus dextrose have little or no effect. Six days of starvation caused no marked change in the rate of alcohol metabolism in dogs, nor was there a change in the rate of utilization by liver homogenates from this species.

Newman (58) has reviewed the effects of insulin on the rate of metabolism of ethyl alcohol and recorded differences of .019% per hour with alcohol alone, .023% per hour with insulin, and .023% per hour with insulin plus glucose. He concludes that insulin does produce a statistically significant increase in the rate of alcohol metabolism either alone or in combination with glucose, and that this effect varies in some degree from test dog to test dog and from time to time.

Since Castex (59) has reported that intravenous succinic acid in amounts of 125 to 300 mg/kg rapidly alleviates alcohol depression and concurrently reduces blood alcohol levels, the experiments were repeated by Hulpieu (60) in animals receiving single administrations, a similar dose divided over short periods of time, and by continual infusion. Under none of these conditions was it possible to demonstrate any effect on alertness or change in the rate of alcohol metabolism. It is suggested that the discrepancy might be due to a state of unequilibrium in Castex' s animals with diffusion of alcohol into the rest of the body. The decrease of alcohol from the blood stream of normal pigeons is .017% per hour; this increases to .025% per hour when the animal is fed a high carbohydrate diet. Production of thiamine deficiency to the point of opisthotonus does not alter the decline of alcohol. In three dogs made thiamine deficient, blood pyruvate and lactate became elevated and administration of 25 cc of 95% alcohol orally resulted in a subsequent decrease in blood pyruvate accompanied by a further increase in blood lactate. After thiamine treatment, alcohol caused a parallel fall in both substances.

Gluco-corticoid preparations, adrenocorticotropic hormones, prednisolone and cortisone have not beem demonstrated to affect alcohol metabolism in dogs receiving repeated intravenous infusions, in subjects administered alcohol in test situations, or in the treatment of patients admitted with acute intoxication. However, without statistical validation the impression has been received that there occurs a compensation in psychological alterations when these materials are administered, and that there follows a more rapid recovery of the acutely intoxicated person.

Jervis (61) has suggested that viatmin C plays a role in the metabolism of alcohol based on a slower rate of utilization in vitamin C-deficient guinea pigs and a lowering of the lethal level. These studies are open to question, based on the small number of animals used.

Alcoholic patients administered alcohol orally and either glucose, emulsified fat or amino acids intravenously, exhibited different rates of alcohol metabolism as measured by the height of the blood alcohol curve and the time for alcohol to disappear from the blood stream. The latter is less in the group receiving amino acids, though in all groups the rate of decline of alcohol from the blood does not differ from the controls. In a parallel experiment, when amino acids in the form of Amigen or Aminosol were administered intravenously one hour following the imbibing of alcohol, the disappearance rate was accelerated.

Rice (62), reporting on 600 post-operative surgical patients who had received 60 cc of 98% alcohol in 1000 cc of fluid together with 5% amino acids and 5% glucose, states that at a constant rate of administration the

blood alcohol levels ceased to maintain the same rate of increase as was observed during the first hours of administration. He concluded that alcohol given intravenously increases the caloric demand, thereby causing a more rapid metabolism of circulating alcohol.

Alcoholic patients free of other pathology or nutritional deficiency, when administered 4 oz of whiskey by mouth and glucose, emulsified vegetable fats or amino acids intravenously, have different maximum blood alcohol levels. The amino acid treatment reportedly affected the rate of alcohol metabolism by lowering the peak of maximum blood level significantly and by hastening the time to reach zero alcohol concentration.

The previous reports have dealt primarily with the intact host. Now let us consider the observations made on isolated tissues and enzyme systems. In 1938 Leloir (63) reported on metabolism of ethyl alcohol in animal tissues, indicating that pigeon liver oxidizes less alcohol than rat liver, and that in the latter species the amount oxidized is lowered by fasting. Oxidation is inhibited by a number of chemicals including cyanide, iodoacetate, fluoride, arsenate, fluoradazine, malonate and oxalate. 2, 4-dinitrophenol increases utilization of low concentrations and decreases it at high concentrations. Also, in vitro butyric, beta-hydroxybutyric, ascorbic acids, glycine, ornithine, ammonium chloride and insulin, exert no action, while glycerin slightly depresses alcohol oxidation.

Dewan (64) demonstrated that preparations made from the brains of various animals so as to contain the catalytic system minus diphosphopyridine nucleotide, did not metabolize alcohol; however, when this material was added, brain extracts took up oxygen readily. He concluded that vitamin B_2 was a component of the alcohol oxidation system acting as a hydrogen carrier between reduced diphosphopyridine nucleotide and cytochrome system. He concluded that this system probably acted as a detoxicating or protective device, and that alcoholics who had poor nutritional intake and were subject to vitamin deficiency, particularly of the B complex, were likely to have alcohol reach the brain in higher concentrations and remain there for a longer period of time.

There is a dichotomy of opinion as to the role that catalase plays in the physiological oxidation of alcohols. Some investigators imply that all alcohol oxidation passes through the catalase-hydrogen peroxide system. Theorell (65) concludes that most, if not all, catalase action is peroxidatic, but that while ethyl alcohol is probably oxidized by alcohol dehydrogenase, methyl alcohol is attacked by catalase. Jacobsen (66) interprets the catalase data to indicate that about one-fifth of ethyl alcohol and all of methyl alcohol are oxidized by catalase. After reviewing all factors, Bertlett (67), based on the above conclusions and data of his own, has hypothesized that

alcohol dehydrogenase medicates the first step in the metabolism of both methyl and ethyl alcohol, but that catalase does not participate in this metabolism.

Burbridge (68, 69) has shown that a number of tissues, including muscle, brain, heart, lung and kidney, as well as liver, can utilize ethanol as a substrate. He found no utilization by blood. Most investigators believe that liver is the major if not the sole organ responsible for alcohol metabolism in vivo. Rat liver homogenates incubated with tagged radioactive ethyl alcohol showed utilization of 10 to 50 mM of alcohol in two hours with production of 6 to 35 mM of acetaldehyde. Addition of DPN enhanced the rate of alcohol disappearance with acetaldehyde accumulation, indicating DPN-dependency of both acetaldehyde formation and utilization. Addition of folic acid at 3×10^{-6} M completely inhibited ethyl alcohol metabolism, as did aminopterin. The effect of the latter two substances would seem to be due to binding of thio linkages in the alcohol dehydrogenase.

Livers taken from fasting rats and from those that are fed, have different in vitro rates of ethanol metabolism. However, the addition of diphosphopyridine nucleotide restores in part the decreased utilization rate of the fasted rats. DPNH re-oxidizers such as methylene blue and ferrocyanide also increase alcohol oxidation rates. In fasted animals both pyruvate and alanine increased the rate. Liver and kidney tissues taken from rats treated over a number of days with insulin did not utilize alcohol at a greater rate, nor was the conversion of the carbon fragments into lipids any different from that of non-treated animals. JB-516 showed an inhibition of ethanol metabolism by rat liver slices, though chlorpromazine and iproniazid were without effect. Cat liver utilizes alcohol at the rate of between 4 and 6 mg/min/100 gm of liver, and varies directly with the concentration of alcohol in the perfusion fluid. Alcohol at .02% or higher in an incubation medium depresses glucose output of liver slices and glycogen synthesis of isolated diaphragm. The glycogen content of the liver, and hence the glucose output of liver slices, is depressed in rats fed 15% alcohol in their drinking water for three to six months, and the glucose uptake of isolated diaphragm is similarly depressed.

Three pathways of alcohol metabolism have been demonstrated utilizing C^{14}- tagged alcohol in vitro, namely conversion to CO_2, to fatty acids and to cholesterol. This may occur with liver, kidney, diaphragm, brain and lung slices. In these experiments no substrate was added to the incubation medium, which ranged in alcohol concentration from .006 to .25%. Liver slices converted from 11 to 26% of ethyl alcohol to CO_2, 1.2 to 4.5% to fatty acids, and a maximum of 1.4% to cholesterol. Kidney slices converted 17 to 29% to CO_2, but only a small amount to fatty acids, and no radioactivity was detected in the cholesterol. Lung also oxidized small quantities of

alcohol to CO_2 and did convert a small amount into fatty acids. Diaphragm was able to convert only a small amount to CO_2 and none to fatty acids or cholesterol. There was no evidence of metabolism by brain since glucose is necessary for the uptake of alcohol. The finding of no oxidation of ethyl alcohol by brain is most likely due to experimental conditions. Oxygen consumption of the cortex medulla, cerebellum and brain stem and that of the immature brain of rats, were all decreased by alcohol as measured in a Warburg apparatus at a concentration of 6% alcohol. The effects of alcohol acidity and of alcohol plus acidity, and the oxygen consumption of excised rat cortex indicate that concentrations of alcohol as high as 3.2 M produce an increase in oxygen consumption, while concentrations over 3.6 M cause a decrease. Increase in the acidity enhanced the inhibiting action of alcohol on oxygen consumption.

Ethyl alcohol has no effect on the ratio of oxidative phosphorylation to oxygen consumption (P/O) in rat brain mitochondria. Acetaldehyde, however, is effective in lowering this ratio in concentrations equivalent to those observed in man during the TETD-alcohol reaction. This depressing action at low concentrations applies only to the system utilizing pyruvate-fumarate as substrates. TETD in concentrations having no effect on mitochondrial phosphorus uptake can act synergistically with effective acetaldehyde concentrations.

The concentration of alcohol apparently influences the rate of uptake by brain and liver. Cosubstrates influence the uptake of alcohol by rat brain, glucose being the most effective. Acetaldehyde uptake is only slightly influenced by alcohol, while its presence decreases ethyl alcohol metabolism. Both pyruvate and acetaldehyde decrease the uptake of alcohol by human brain tissue. It is possible that there are regional as well as species differences. The rate of metabolism in the liver plateaus at approximately .26%, while brain does not show any appreciable metabolism until .1% is obtained, and levels off at .35%.

Based on failure of artery and vein CO_2 and O_2 levels to be altered significantly by patients in insulin shock who received alcohol, Goldfarb (70) concluded that the human brain does not oxidize ethyl alcohol to any appreciable degree. This is in contrast to the *in vitro* results reported by Sutherland (71) using human brain slices, and by other experiments in animals. As indicated above, the first step in alcohol metabolism is conversion to acetaldehyde. While the further utilization of acetaldehyde is not a rate-influencing factor in metabolism of alcohol by the liver, it does appear to influence uptake of ethanol by other tissues *in vitro*. Therefore, a few observations on acetaldehyde metabolism seem pertinent.

Administration of acetaldehyde to dogs results in the appearance of alcohol in the plasma in concentrations between .4 and .9 mg%. If pretreated with TETD, the alcohol concentration may rise to 2 mg%. Optimum acetaldehyde metabolism in rabbits as determined by perfusion experiments, is about 2 mg/min. The rate seems to be constant, but the concentration in the tissues required to metabolize the same amount of acetaldehyde in TETD-treated animals is higher than in untreated animals. The capacity of the rabbit liver to metabolize acetaldehyde does not exceed 10 mg per 100 gm of liver. It has been established that TETD does not affect alcohol metabolism, but only that of acetaldehyde. No significant differences are found in the acetaldehyde concentration of animals treated with TETD in comparison with the controls. No production of acetaldehyde has been observed in isolated livers or hind limbs of TETD-treated or untreated animals. It has been concluded that very little, if any, acetaldehyde is formed during normal metabolism, and alternate pathways in the metabolism of acetaldehyde do not play a significant role.

Levels of acetylcholine and acetoin which occur in the brain during acetaldehyde intoxication show a time-dose response. After three minutes a moderate increase in the level of acetylcholine and a marked rise in acetoin levels occur. Ten minutes later the acetylcholine elevation is still apparent, but the level of acetoin is restored to control values. The same is true at 30 minutes thereafter. Since acetoin has not been found to be metabolized by brain preparations in vitro, its rapid decline is presumed to be due to its removal from the brain and destruction elsewhere in the animal. Symptoms of intoxication persist in animals treated with acetaldehyde, although brain levels of this substance are normal. It appears, therefore, that symptoms of acetaldehyde intoxication are not due to elevated levels of acetylcholine or acetoin. It has been suggested that the effects of alcohol intoxication are due primarily to the presence of acetaldehyde.

The lower aliphatic alcohols, including ethyl alcohol, have been demonstrated to have no effect in vitro on the coupling of oxidative phosphorylation in concentrations high enough to produce marked toxic effects in vivo. This is in distinction to ethyl ether, which is capable of this uncoupling reaction. It may be concluded that the failure of alcohol to affect important functions of the intracellular mitochondrial particles indicates that the response to ethanol in the intact cell is probably elicited by its action on the plasmatic membrane. In distinction, acetaldehyde has an effect on phosphorus uptake at levels approaching those which exist in man during the TETD-alcohol reaction. The activity apparent at this low concentration which shows depressant activity to mitochondrial function, suggests a relationship between this action and the narcotic effect of the compound.

This is of particular significance in view of the known relationships between ethanol and its breakdown to acetaldehyde in the course of metabolism in the body.

Symptoms of acetaldehyde intoxication in animals are similar to those of alcohol intoxication, though fractional doses given at 15 minute intervals in a total cumulative dose that would cause lethality, do not kill the animal. Ten minutes after the last dose, the blood acetaldehyde concentration is only .07%.

Toxicology

The toxicology of acute alcoholic intoxication has been referred to briefly. The subject will be further expounded at this point, prior to discussing the role of other depressants of the central nervous system which, from a practical standpoint, may be of significance in potentiating the effects of alcohol. Four types of alcohol poisoning are encountered. These are acute alcoholic intoxication, post-alcoholic coma, a syndrome associated with chronic cortical atrophy, and the acetaldehyde syndrome resulting from concurrent ingestion of alcohol and drugs which interfere with acetaldehyde metabolism.

Serious acute alcoholic intoxication is characterized by a progressive depression of all vital functions. The rate of respiration becomes markedly slowed, sometimes not exceeding six per minute. There is a dilatation of peripheral and splanchnic blood vessels and a progressive fall in blood pressure. The cardiac rate is generally increased, and body temperature becomes subnormal. Hypostatic pneumonia and increased intracranial pressure occur after about 10 hours. Secondary infection may compoicate the picture. The usual outcome is favorable if therapy is instituted. This condition generally follows ingestion of a total quantity of alcohol equivalent to 3.0 to 4.0 cc/kg body weight consumed over a short period of time.

In addition to this type of uncomplicated acute ethyl alcohol poisoning, acute intoxication is a contributing or underlying factor in a large percentage of cases of suicide, homicide, trauma, poisonings, and medical and surgical fatalities.

Lethal Levels

Linck (72) reported on lethal levels in 125 persons who died of alcohol poisoning. These levels ranged between .35 and .50%. In the case in which death occurs as a result of complications, such as suffocation or

aspiration of vomitus, the levels were as low as .20 and .35%. Death usually occurred eight hours after the last drink in cases without complication, and in as short a time as two to four hours in complicated cases. The amount of alcohol consumed varied between 200 and 1000 cc of 40 to 50% alcohol, and Linck calculated that the lethal dose for man is approximately 3 gm of absolute alcohol per kg of body weight.

In examination of 84 fatalities in which all recognizable common causes of death except acute alcohol intoxication were ruled out, Kaye (73) determined that the majority of blood alcohol levels at death were between .25 and .50%. Death did not necessarily occur at the peak concentration, based on knowledge of survival time. Utilizing the standard rate of disappearance of alcohol of .02% per hour, it was estimated that death was generally unavoidable if the blood alcohol reached .50% at some time during intoxication, and was probably due to irreversible and progressive injury to the central nervous system. Reports from one medicolegal jurisdiction indicate that levels of alcohol in the brain in fatal cases occurring in the asphyxial stage of intoxication may be as low as .23% when other pathological conditions such as coronary sclerosis are present.

Occasionally high levels of alcohol in the blood are reported at death. Kohn-Abrest (74) indicated that in approximately 40% of his cases, cadavar blood alcohol concentrations exceeded .8%. However, lethal concentrations of alcohol in the blood are usually accepted as .5%. Jetter (75) examined 2000 cases in which antemortem blood samples were taken, and no incidence was encountered in which death did not occur if the concentration reached this level. In only three of these cases was the postmortem alcohol concentration higher than .5%. In these cases death occurred soon after the onset of coma. However, death may occur several hours or even days after the onset of coma. When death occurs more than 24 hours after the ingestion of alcohol it is unusual to find elevated postmortem blood levels. Anatomical abnormalities at autopsy in most cases are non-specific and inadequate in themselves to explain death. As previously reported, the frequency of alcohol as a primary cause of death varies in different parts of the world and at different times. An analysis of fatal alcohol poisonings in Finland certified at postmortem examination between the years 1920 and 1949, showed that during the Prohibition years of 1922 to 1932 the death rate from this cause was higher than in subsequent years. However, in 1949 it has increased five times from its pre-war level. These deaths account for 43.4% of all accidental poisoning, presenting a rate of 1.76 deaths per 100,000 of population.

In Massachusetts, on the other hand, during a 10-year period from 1928 to 1937, approximately 10% of all medical examiners' cases (8,661) were

due to toxic substances. Ethyl alcohol caused more deaths than all other toxic substances put together, being responsible for 52%.

The lethal dose varies only slightly among different species, but can be affected by a number of experimentally induced factors. The lethal dose of ethyl alcohol for dogs is 9.6 ± 1.6 ml of absolute alcohol per kg of body weight. With few exceptions the animals die during the time the blood alcohol concentration is declining. This is particularly true in animals surviving longer than 12 hours, and in these cases there is a progressive decrease in blood pressure, resulting terminally in circulatory failure. In the majority of animals, however, the intoxication is related to respiratory failure. A number of biochemical and physiological changes are attendant upon these doses and there is noted a hyperglycemia and an increase in hematocrit, hemoglobin and plasma non-protein, with a decrease in blood pH and sedimentation rate. Oliguria, and in many cases anuria, are noted after the animals become comatose. Other investigators report that lethal blood alcohol concentrations in dogs, guinea pigs and mice range between .85 and 1.45% in the blood, with a mean of 98%. This is irrespective of the type of beverage used and it is concluded that the congeners present do not affect the toxicity of alcohol.

The effective concentration at respiratory failure in a series of fasted rats was .93% of alcohol, with extremes of .89 and 1.0% in the blood. The concentration of alcohol in the blood, causing death, is the same for animals breathing oxygen and breathing air. However, inhalation of dilute carbon dioxide caused a definite increase in the concentration of alcohol required to cause death. In non-toxic doses caffeine, phenacetin, antipyrine and aspirin were without effect.

The amyl alcohols are approximately 12 times as toxic as ethyl alcohol for rats and dogs. The major metabolites of the primary amyl alcohols are aldehydes. The secondary alcohols are converted to ketones which disappear from the blood more slowly than the alcohols.

The average blood alcohol concentration causing death of dogs perfused at a rate resulting in slow but gradual blood alcohol content, was .69%. The age of mice is a determining factor on the toxicity of alcohol for that species, a significant difference existing between animals that are 4 and 6 months old and those that are 12 and 24 months old.

Mortality varies somewhat with the concentrations of aqueous solutions of alcohol used, being the greatest with 60% and less with other dilutions or concentrations. This phenomenon is explained on the basis of poor absorption because of coagulation of the peritoneal surface, the material having been given intraperitoneally. When 9.5% ethyl alcohol is consumed

by mice in their drinking water for 19 days and the animals are then challenged intraperitoneally with a single dose of 48% alcohol, mortality is decreased from 62% to 36%, suggesting an increased resistance in habituated animals.

When measured on goldfish placed in an environment of an aqueous solution of a series of alcohols, the butyl alcohols were found to be approximately five times as toxic as ethyl alcohol, the propyl alcohols three times as toxic, and the methyl alcohols one-half as toxic. Narcotic effects generally followed the same order, though there was more variation in the results.

The observations of most investigators lead to the conclusion that peak toxic activity is reached at about the C_6 level and declines thereafter.

Tissue Changes

Gross and microscopic findings are non-specific in acute alcoholic intoxication. The most constant pathologic changes are severe meningeal and cerebral congestion, pulmonary edema, acute gastritis, visceral congestion, and sometimes pancreatic necrosis. These changes are found in other conditions, especially those characterized by anoxemia. A number of specific changes have been reported in the nervous system of patients exhibiting various syndromes associated with chronic alcoholism. Brain taken from chronic alcoholics and examined at autopsy frequently shows atrophy, notably in the frontal lobes. Microscopically there is an appearance of neuronitis of the peripheral nerve fibers and a syndrome characterized by small foci with degenerative change in the vessel walls and subacute necrosis of the parenchyma. These changes are probably due to extreme depletion of B_1 and overabundance of other vitamins. Lesions found in acute alcoholic encephalopathy are similar to those which appear with avitaminosis, starvation and malnutrition. A fair proportion of cases showing signs of alcoholic encephalopathy during life have but few demonstrable lesions in the brain, and these, therefore, may be due to vascular or chemical changes in the nervous system.

Gross and microscopic examination of brains of 12 patients with Wernicke's disease who were chronic alcoholics, showed changes identical to those in pigeons suffering from vitamin B_1 deficiency. It was concluded that angio-degeneration with varicose deformity of the vascular bed is a primary change. A case of primary degeneration of the corpus callosum confirmed histologically was reported in a 67-year old chronic alcoholic in 1942. This was the second such case of its kind appearing in the medical literature in America. It is suggested that this is due to a deficiency of the

vitamin B complex. Cerebellar changes described as cortical or intracerebellar atrophy, were reported in five male patients with excessive alcoholic intake, but without edema, pellagra or peripheral neuritis.

Action with Other Drugs

The simultaneous ingestion of alcohol with other hypnotics, alcohols, narcotics, or concurrent exposure to other toxic chemicals creates problems for the law enforcement officer regarding the necessity for apprehension and custodial care, and of diagnosis and therapeutics for the practitioner. Under such circumstances, behavior may become markedly deranged and the clinical picture confusing. A discrepancy appears to exist between the level of alcohol present in the body fluids and breath, and the degree of coordination, mental competence and physiologic depression. The question arises as to the possibility of synergism. Synergism is defined by Gruber (76) as "the cooperative action of discrete agencies such that the total effect is greater than the sum of the two effects taken independently". The terminology used by pharmacologists and practitioners is not always clear in this respect. For our purposes we will distinguish this phenomenon from potentiation, which we will consider as the situation in which one agent shows no particular effect on a system, but exaggerates the effect of another, and from addition, which connotes the sum of the fractions of two independently effective doses.

The first materials to be considered are congeners, a number of which have been found in alcoholic beverages. These include fusel oil, acids, esters, aldehydes, furfural and tannins. These contribute principally to taste and bouquet. Whether or not any of them are undesirable in terms of hangover or other aftereffects is yet to be determined. In the evaluation of their possible effect on the physiological action of alcohol, it has been determined that respiratory failure occurs at about the same concentration of blood alcohol when any of 64 distilled spirits were administered to rats. While the amount of alcohol required to produce respiratory failure for any one spirit was generally the same, the amount required of various spirits was considerably different in quantity. This suggested that the congeners might have some effect on either excretion or the rate of metabolism. When different spirits were used but the same amount of alcohol was given, the length of time required for the disappearance of alcohol from the blood was greatest for the more toxic spirits and least with the less toxic spirits. It was also noted that chemical treatment of various spirits to remove the congeners, making them less toxic, also increased the rate of metabolism of the alcohol.

Methyl and isopropyl alcohols, especially the former, are consumed with and appear as a contaminant of illegal alcoholic beverages. Poisoning from methyl alcohol was especially common during the prohibition era and during World War II. Both alcohols produce an effect on the nervous system similar to that of ethyl alcohol, though methyl is somewhat less potent than ethanol and isopropyl more potent. In addition, methyl alcohol produces a marked acidosis with signs of motor restlessness, clammy extremities, diarrhea and symptoms of headache, vertigo, blurring of vision and muscle pain more pronounced than the signs and symptoms of inebriation. The specific toxicity for the optic nerve is characteristic. Persons acutely intoxicated by methyl alcohol generally do poorly, though there is some evidence that when ethyl alcohol is simultaneously consumed the prognosis is somewhat better, due to the competitive displacement of methyl alcohol from receptor sites by the ethyl alcohol. This serves as the basis for Roe's proposed therapy of methanol intoxication (5). Inebriation from isopropyl alcohol is longer and more intense, due to the slower rate of metabolism of isopropyl alcohol, its greater potency, and the fact that its metabolite, acetone, is also mildly narcotic.

Methyl alcohol in amounts varying between .001 and .01% were present in 25% of a small series of medicolegal cases examined in France in 1949, which compared favorably with its presence in 50% of the cases in 1948. The interpretation is made that the liquor was improving in quality, since the trace amounts of methyl alcohol could be considered as evidence of the consumption of "bad spirits".

Cerebral blood flow and metabolic ratio in persons intoxicated with methyl alcohol are lowered, and confirm the hypothesis that oxidative processes of cerebral cells is impaired in this intoxication.

Scrap iron is a term used to designate an alcoholic beverage containing 20 to 40% ethyl alcohol, 15 to 25% isopropyl alcohol and naphthalene. It has a peculiar metallic taste, is cheap and highly intoxicating. Twenty-six persons drinking this beverage developed an acute brain syndrome with symptoms identical to delirium tremens. All recovered with an average hospital stay of 8.6 days. However, five patients had a chronic brain syndrome. The severity of psychotic manifestations is out of proportion to the quantity of alcohol consumed. It is concluded that prolonged drinking of scrap will produce effects similar to alcoholism, but of a more severe degree and within a shorter period.

The handling of the acute alcoholic during the excitement phase of his intoxication poses problems, since the use of hypnotics and depressants necessary to achieve control of the excited patient must be balanced against the depression produced by the administration of additional sedatives to an

already physiologically depressed person. Paraldehyde is an effective and time honored agent in the control of the acute alcoholic. However, Weatherby (77), commenting on the instance of death attendant upon the use of paraldehyde in cases of acute alcoholism, concluded that there may be some synergistic effect between the two substances. Following administration of fractional doses of the LD_{50} of both paraldehyde and alcohol intraperitoneally in mice, he noted that when varying concentrations of these fractions were given in a single combined dose, more than an additive action occurred. When the two substances were given not in combination but at varying sequential time intervals, there was a difference in mortality if alcohol were given first, probably due to the more rapid elimination of paraldehyde in the reverse situation.

Two cases of sudden death following the administration of 10 and 40 cc of paraldehyde respectively, to two alcoholics were reported in 1954. The events were stated to possibly be related to potentiation by alcohol or to aggravation from liver damage secondary to chronic alcoholism.

Steyn (78) has advised that paraldehyde should not be used in the treatment of delirium tremens, based on his belief that though alcoholics are more tolerant to the drug's sedative action, it may also act as an excitant and aggravate the condition.

The barbiturates are unduly used and abused by alcoholics. They also serve as a part of the therapeutic regimen for handling acute intoxications in hospitals caring for these cases. Synergism between barbiturates and ethyl alcohol has been demonstrated through a number of experiments. These have included mortality and recovery time from hypnosis in mice, reduction in the quantity of barbital required for anesthesia in dogs, the duration of anesthesia in rabbits, and the quantity of picrotoxin necessary to antidote the depression. The minimal dose required to cause anesthesia in these animals is markedly diminished by the presence of alcohol, and anesthesia is definitely prolonged when the interval between alcohol and barbiturate administration is reduced, despite approximately equal blood alcohol levels. In addition, experiments on the relative analeptic activity of picrotoxin also indicate synergism.

Synergism has also been demonstrated between each of six short-acting barbiturates and alcohol, as demonstrated by signs and duration of intoxication in mice. The coefficient of synergism was highest for hexobarbital. Responses at diminished doses of barbiturates and alcohol especially suggest a synergistic rather than additive effect. Phenobarbital and alcohol in combination are reported to produce symptoms of impairment which could correspond to blood alcohol levels approximately 75% higher than the actual ones.

In contrast, Gruber (79), utilizing both short- and long-acting barbiturates, and measuring sleeping time and mortality as an end-point, concluded that there occurs no unpredictable distribution between the effects of varying doses of alcohol and barbiturates which suggests synergism. Other data on animals also support Gruber's conclusions. The matter does not seem to be capable of finalization at present.

The question as regards synergism with tranquilizers also appears unresolved. Utilizing sleeping time in mice after administration of various doses of alcohol and of alcohol plus chlorpromazine, as a measure of potency, it has been demonstrated that potentiation is apparent with small doses of the tranquilizer drug. This procedure leads to prolongation of sleeping time in the order of 500%. The duration of the chlorpromazine effect is about 30 hours at 10 mg/kg, and is greatest 1.5 hours after oral administration. Repeated administration of the test diminished the potentiating action somewhat.

Employing a battery of tests to measure coordination and judgment, Zirkle (80) demonstrated a difference in performance among patients receiving alcohol sufficient to give a blood level of .05%, chlorpromazine in amounts of 200 mg, and various placebos. Detriment in performance was greatest in the test group having both alcohol and chlorpromazine. Performance on high level tasks was reduced to a greater degree than performance on low level tasks. Ratings of their own performance by subjects correlated well with test results. Greater impairment from the combination of the drugs than from one taken singly, was recognized by subjects. Based on this, Zirkle recommended that physicians who prescribed chlorpromazine should warn their patient of the possible dangers attending even moderate drinking. This may be dangerous when taking tranquilizers, due to the higher blood level reached and the slower rate of metabolism of ethanol, in addition to the synergistic depressant effects.

Administration of sublethal quantities of serotonin, tryptamine or dopamine 30 minutes prior to an hypnotic but nonlethal dose of ethanol, induced mortalities of 83, 57 and 50%, respectively, as well as causing a decisive prolongation in the sleeping time of survivors. Further, administrations of as little as .06 mM of these substances, an amount which provoked few somatic behavioral effects per se, when administered to mice pre-treated with alcohol caused a marked potentiation of the latter's narcotic action.

Chlorpromazine at 2 mg/kg, iproniazid at 10 mg/kg, and JB-516 at 3 mg/kg, all exerted potentiation of the depression caused by doses of ethyl alcohol in vivo. Chlorpromazine and JB-516 also caused a marked lowering in the rate of alcohol clearance in the blood of dogs. Part of the

effect of the phenothiazine type of tranquilizer appears to be due to its effect on alcohol metabolism.

Betlheim (81) reported that it was possible to produce delirium and hallucinations in 20 alcoholic patients under control conditions by the administration of subnarcotic doses of hexobarbitone. The effects of the drug included altered motor activity, infantile behavior, confabulation, and delusions. He rendered the opinion that hexobarbitone increases suggestibility of the alcoholic patient, and therefore the treatment of alcoholic patients with barbiturates is at times inadvisable.

In conditioned response tests in rats, meprobamate, chlorpromazine and pentobarbital all significantly potentiated the effect which alcohol alone exerted on anxiety. Discrimination was significantly reduced by alcohol alone, the same three drugs alone, and phenaglycodol. All four drugs also significantly potentiated the effect of alcohol on discrimination. Alcohol significantly decreased the ability to respond to stress. Meprobamate, phenaglycodol and chlorpromazine (the latter having no effect by itself) all significantly potentiated the action of alcohol in this respect. It may be concluded that this potentiating effect of tranquilizers makes their use undesirable by those persons ingesting alcohol.

Significant quantities of alcohol are found in approximately half of the persons who die from accidental carbon monoxide intoxication, as judged by this author's experience with 100 fatal cases. There is no reduction in the percent saturation of hemoglobin in the alcoholic as compared with the non-alcoholic cases. The role of alcohol, if any, seems to be to increase the risk of accidental exposure through decrease in coordinated and thoughtful behavior. Some investigators studying patients who had suffered acute carbon monoxide poisoning believe that after drinking, blood alcohol curves will be higher by about 20% than curves of normal persons drinking the same quantity of alcohol. Investigators also suggest that central nervous system damage due to the monoxide exposure may account for lowered alcohol tolerance. Bjerver and Goldberg (82) studied 11 subjects who had residua from exposure to producer gas, a fuel for motor vehicles used in Sweden during World War II, which contained 30% carbon monoxide, and found that there was no difference in tolerance, rate of disappearance of alcohol from the blood, distribution in the body, or rate of oxidation, as compared with normal unexposed persons. The authors maintained, however, that theoretically a severe head injury may lead to an alteration in threshold or level at which intoxication from alcohol ingestion will appear.

In experiments evaluating chronic exposure, dogs which were repeatedly administered alcohol by mouth to achieve concentrations of .15% and then exposed to carbon monoxide at .01% by volume for six hours five days a

week, showed no cumulative effects as measured by liver function tests, electrocardiograms, or hemoglobin measurements.

Amidon by injection is reported to have potentiated the effect of alcohol, the total concentration being .125%, with resulting death due to respiratory paralysis. In animal experiments it has been established that the combined effects of the drugs is additive and not potentiative.

Most of the data relative to the effect of narcotics has been derived from animal experiments, since the narcotic addicts and the alcohol habitues seldom resort to the use of the alternate drug. Based on the experience of Naalsund (83), however, morphine is contraindicated after the ingestion of alcohol since even therapeutic doses of morphine have been observed to precipitate violent symptoms.

Mice administered alcohol orally and morphine subcutaneously exhibited effects especially with regard to mortality, which showed that potentiation occurred. The potentiation was more distinct with small than with large doses, being approximately three times as great as expected with mortalities of 10 to 25%, and less at higher concentrations. Mice treated with combinations of various fractions of the LD_{50} of amidon and alcohol showed additive and not synergistic effects. Clinically, a young adult who had a blood level of 32.5 mg died of respiratory paralysis. Synergism was suspected.

Rats which had been exposed to alcohol for 15 hours and though in an adaptive state, showed no visible effects of alcohol intoxication, but became markedly so after receiving 10 mg of apomorphine. There was an accompanying shift in the direction of diminished excitability of nervous tissue as measured by chronaxies.

The effects of alcohol in combination with a variety of other drugs and chemicals has been reported. Wilson (84) advises that persons exposed to carbon disulfide should not drink alcoholic beverages, based on the neurotoxic effects of the former substance. In a double blind randomized study with 24 subjects, methapyrilene and 6.5 oz of whiskey had no potentiating effect on the excitement or social disinhibition produced by alcohol. Adams (85) studied the comparative toxicity of chloral alcoholate and chloral hydrate by determining the hypnotic potencies and acute and chronic toxicities. He concluded that there was no support for the impression that a solution containing alcohol with chloral hydrate was particularly potent because of the formation of an alcoholate. Pretreatment with ethyl alcohol prevents the formation of trichloroacetic acid from trichloroethanol and also inhibits the oxidation of chloral hydrate to trichloroacetic acid. It is

concluded only that ethyl alcohol and these latter substances share a common pathway of metabolism.

Vasomotor symptoms have been reported to appear after the ingestion of alcohol in persons previously treated with animal charcoal. This was noted as early as 1917. The syndrome consists of deep reddening of the face and extremities and increased pulse rate, dyspnea and a decrease in blood pressure without nausea or vomiting. The severity depends on the dose of both alcohol and charcoal. The dynamics of the sensitizing effects are unexplained.

Isoniazid has been reported to cause severe intoxication by as little as one bottle of beer, indicating an intensifying effect. An epidemic of epileptiform convulsions is reported in a tuberculosis sanitarium among chronic alcoholics given isoniazid. Caution is admonished regarding use of alcoholics given isoniazid. Caution is admonished regarding use of alcoholic beverages by persons on this therapy.

Rabbits administered alcohol and sodium arsenite all died in narcosis within 20 hours, whereas the equivalent dose of arsenic by itself resulted in recovery of animals within 90 minutes. It was concluded that arsenite potentiates the toxicity of alcohol and increases its duration of action, but that the effect was non-specific and due only to additive toxic effects.

When adrenalin is administered before giving a significant dose of alcohol, the depressant action of the alcohol is greater. An increased permeability of the vascular system has been suggested as an explanation. Other explanations relate to the vasoconstriction of vessels in striated muscles which reduces their blood supply and consequently results in a relatively high concentration of alcohol in the blood reaching the brain. The dose of adrenalin necessary to produce this effect is far greater than the amount released under stimulation or excitement.

Epinephrine administered to rabbits in amounts capable of physiologically altering the distribution of alcohol administered intravenously, causes for a short time a condition in which the muscles of the animals contain practically no alcohol. The concentration in their blood and brain becomes extremely high. It is concluded that the "auxoneurotropic" action of adrenalin is explainable by alteration in circulation.

γ-Aminobutyric acid does not cause death or an increase in periods of hypnosis in alcohol pre-treated mice. Alcohol is stated to cause reoccurrence of dinitrobenzene poisoning long after the disappearance of all symptoms, and persons working with these compounds are forbidden to drink alcoholic beverages. The test has been used for diagnostic purposes. The

mechanism of the toxidynamic effect of alcohol is not known. Dogs which had received 1 ml of 98% alcohol per kg of body weight daily for four months were not adversely affected by 10 mg of m-dinitrobenzene. Larger doses of alcohol or longer periods of alcoholization produced varying results on subsequent administration of m-dinitrobenzene. Additive effects of alcohol and m-dinitrobenzene on the central nervous system have been demonstrated in rats.

Agents Causing Unusual Responses

A number of drugs are known to produce disagreeable symptoms when taken in combination with alcohol. Among the more common ones are calcium cyanamide and tetraethylthiuram disulfide (TETD). The lethal dose of the latter in animals is about 3 gm/kg. Sensitivity to alcohol produced by a single dose of .5 gm of TETD may last three to four days, and 1.5 gm will produce sensitivity up to eight days. As evidence of this sensitivity there is a marked increase in ventilation, of the respiratory dead space, and of oxygen consumption, a slight increase in cardiac output, and a decrease in alveolar carbon dioxide. Accompanying this is a flushing of the face, dilatation of scleral vessels, palpation, a "bull-eyed" look, vomiting and headache. These symptoms generally appear 7 to 12 minutes after alcohol intake, become maximal after 30 minutes, and disappear in one to two hours. While flushing is noted at blood alcohol levels of .015 to .02%, pulse rate changes usually occur only above this level. The reaction is accompanied by the formation of acetaldehyde in the organism in greater quantity than when alcohol is ingested in the absence of TETD. Similar effects are produced by the slow infusion of a 5% solution of acetaldehyde into the vein of human subjects to give a blood acetaldehyde level of 0.2 to 0.7 mg%. The syndrome, first described by Hald and Jacobsen (86), has since been observed by hundreds of investigators and clinicians. The maximum acetaldehyde level in the blood reached during an alcohol-antabuse reaction is 660 μg% for mild reactions, and 1000 μg% with moderate reactions. Generally the peak of the acetaldehyde curve corresponds with the peak of the alcohol curve. When the dosage of TETD is kept constant and the amount of alcohol varied between .6 and .4 gm/kg, the acetaldehyde concentration in the blood rises with an increase in the alcohol concentration. In animals the highest acetaldehyde concentration occurs when the alcohol is administered about 12 to 18 hours after the drug. Because of the occasional severe reactions obtained in the alcohol-antabuse test demonstration, the procedure is advisedly carried out only at a hospital and under strictly controlled conditions. The patient should remain under observation for at least several hours after the reaction to alcohol has subsided.

TETD has been reported to have pharmacologic effects of its own in addition to its sensitizing effects. These include a sedative effect, decrease of insomnia, and alleviation of nervous and emotional tension, but often itself leads to drinking. Up to 1 gm of body weight of TETD does not significantly increase the sleeping time of mice administered 30 mg/kg of thiopental. A prolongation of sleeping time is achieved in rats given a similar dose of thiopental and half the dose of TETD. There may be a difference not only between species, but also between strains of the same species

The metabolism of TETD as investigated by means of radioactive sulphur, indicates that 10% of an ingested dose is excreted in the feces, while the rest is absorbed. The greatest portion, about 45% of an ingested dose, is excreted in the urine as free and esterified sulfate, only small quantities of the unchanged drug being present. Metabolism of the drug yields a diethyldithiocarbamic acid. Optimum therapeutic levels are between 0.5 and 1 mg of TETD per 100 ml of plasma.

Blood perfused through livers taken from animals pretreated with TETD give high acetaldehyde levels when alcohol is added, reaching concentrations of 4.5 mg%. The inhibitory effect of TETD on acetaldehyde dehydrogenase of liver is reversed by low concentrations of reduced glutathione, and by high concentrations of ascorbic acid. The affinity of the enzyme protein to TETD is approximately 350 times its affinity for acetaldehyde.

The enzymatic oxidation of 2-amino-4-hydroxy-6-pteridylaldehyde was observed to be markedly retarded in vitro by the absence of as little as .06 μg of TETD per ml. Reduced TETD had no inhibitory effect, indicating that the -S-S linkage constitutes the inhibiting part of the molecule. The inhibition appears to be of a competitive nature.

Biochemically the antabuse reaction is explained by fixation of antabuse to the aldehyde oxidases in the liver. For this reason oxidation of acetaldehyde formed during alcohol metabolism is delayed, with a subsequent increased acetaldehydemia. Biochemical alterations accompanying the TETD reaction include a decrease in pH in both arterial and venous blood and a fall in arterial CO_2 of 3 to 8%; acetaldehyde levels may reach 1.58 mg%. TETD has a far-reaching inhibitory effect on respiratory enzymes, approaching in vitro that of cyanide. Oxygen uptake by homogenated rat liver is decreased 85%. The effect of TETD on the toxicity of various aldehydes is varied. There is no increase in mortality from a combination of TETD with acetaldehyde, acrolein or crotonaldehyde, a slight increase with butyraldehyde, and a marked increase with formaldehyde and propionaldehyde.

Fujiwara (87) reports that in habituated rabbits alcohol reaches a higher maximum more rapidly in the blood stream and disappears faster than in non-habituated animals. Moreover, pretreatment with TETD causes a still higher maximum through a delay in alcohol oxidation, both in habituated and non-habituated animals.

In addition to TETD, other drugs and chemicals have been observed to increase the acetaldehyde level after alcohol ingestion. These include bone charcoal, Atabrine, chloramphenicol, trichloroethylene and aminopyrine. Doses producing comparable degrees of sensitization are 1 mg/kg for calcium carbamide, 5 to 10 mg for TETD and 120 to 125 mg/kg for animal charcoal. Vegetable charcoals and purified animal charcoals do not have a sensitizing action. Increased blood acetaldehyde occurs in dogs and man administered animal charcoal. The ingredient which is responsible for sensitization is unknown. It is heat sensitive. In a search for drug with TETD activity, Boyd (88) examined over 70 agents, unsuccessfully except for tolazoline.

The hypoglycemic sulfanilylureas, carbutamide, tolbutamide and chlorpropamide, all reproduced intolerance to alcohol in doses from 65 to 250 mg/kg. The vasodepressor phase of blood pressure of cats injected with acetaldehyde was greater by an average of 16 mm in the presence of these agents. The response to epinephrine was unchanged, however. Glucose in amounts sufficient to correct hypoglycemia can reverse the carbutamide-induced potentiation of the hypotensive phase. Cardiovascular changes seemed to be caused by interference with some glucose-dependent function which is affected by tolbutamide but not by insulin, and it does not seem to be related to an adrenergic blocking mechanism. In one instance, n-Butyraldoxine, a constituent of ink used in color printing, produced an unpleasant response among employees of a printing plant when they drank alcoholic beverages. On examination it was found that the acetaldehyde blood levels were elevated by this substance and that this level was further markedly elevated after the ingestion of alcohol.

Occasionally unusual responses to TETD have been reported when alcohol was not ingested. These have occurred following massage with rubbing alcohol and after ingestion of vinegar which was partly "fermented". TETD has minor effects in combination with other members of the anesthetic and hypnotic drugs. Fifty rabbits receiving 0.5 gm/kg of TETD 16 hours before anesthesia and subsequently anesthetized with nitrous oxide, cyclopropane, pentothal, procaine, ether and Avertin, failed to show an increase in acetaldehyde levels.

TETD produced a potentiation of paraldehyde-induced sleeping time at the dose of 50 mg/kg of body weight, and also raised the blood paraldehyde

level in dogs. In part, prolongation of hypnosis is attributable to retardation in the rate of paraldehyde metabolism. This may be an indirect effect, since acetaldehyde levels are also elevated and there may be an equilibrium between the paraldehyde and acetaldehyde.

TETD has been reported to potentiate the duration of action, but not the depth, of anesthesia produced by barbiturates, though there is a considerable variation from animal to animal and from species to species. Inhalation anesthetics, since they do not take place in the metabolism of the organism, do not share this potentiating effect, and in the case of man no potentiating effects of barbital anesthesia have been reported with TETD. However, in chloroform anesthesia, there is an increase in acetaldehyde levels, presumably due to the small traces of alcohol present as a stabilizing agent in this anesthetic. It is recommended, therefore, that when Pentothal, chloroform or Trilene anesthesia is administered, increased percentages of oxygen and intravenous drip of glucose and ascorbic acid should be used in patients on TETD therapy.

On chronic congestion TETD is reported to give an incidence of fatigue in 36% of the cases, drowsiness in 11%, indigestion in 12%, headache in 8.5%, vertigo in 8.7%, and decreased potency in 9.7%. More side effects in terms of sensation of heaviness in the head, memory alterations and apathy occur with TETD than with calcium carbamide. A toxic confusional state with depressional features has been reported in two patients on TETD therapy. A rare complication of TETD therapy is polyneuropathy. The disorder which developed in six patients over a 12-month period was believed to be due to interference with absorption and utilization of essential vitamins. Symptoms invariably disappear on the discontinuation of the medication.

Linden (89) reported on a severe reaction to TETD. The patient suffered a severe heart attack, convulsions, became comatose, and required hospitalization. Five verified cases of death following TETD-alcohol reactions were reported in Finland in 1957. In one case the TETD was felt to be a primary toxic substance. Four unexpected deaths among 11,000 patients treated with TETD have been reported in Denmark after 3-1/2 years' use of this drug. None of the patients who died showed any evidence of liver damage. It may be that death resulted from factors quite apart from the treatment.

Electrocardiographic tracings taken in a healthy 35-year old man with a negative physical history and no signs of organic disease during a TETD reaction, showed evidence of supraventricular tachycardia with slurring of T-2, depressed RST-3 and inversion of T-3. These signs suggestive of cardiac ischemia indicate the need for caution in the use of TETD.

Amaral (90) further reports hemiplegia and motor aphasia of several days' duratior during an antabuse reaction. Furtago (91) reported circulatory collapse and death of a patient who had undergone an antabuse reaction and at autopsy cerebral hemorrhages were found. Six percent of the electrocardiograms taken in a series of patients, examined by us, receiving TETD therapy and undergoing an antabuse reaction test showed significant EKG changes. In two of these the changes were suggestive of myocardial ischemia in one of the shifting sinus and nodal rhythms in which no P waves were evident. Several severe reactions occurred, with a fall of diastolic pressure to less than 50 in one-third of the patients. In one case the blood pressure dropped to 60/0 and was unobtainable for 10 minutes. A definite myocardial infarct occurred in a male patient, aged 45, after he drank nine ounces of ale containing 5.7% alcohol. Cardiac decompensation appears to be a contraindication for the use of TETD. The drug should never be administered without the knowledge and consent of the patient.

Numerous antidotal procedures have been employed in a study of suitable therapeutic measures for aborting or ameliorating the TETD-provoked reaction, and for possible clarification of the mechanism of action. Iron injected intra-venously in amounts of 13 mg in an iron preparation called "Ferroscorbin" can exert such an effect on antabuse-alcohol toxicosis. It will cause the disappearance of visible symptoms in two to five minutes when present, and can postpone the onset of the reaction if given prior to the administration of alcohol. The mechanism is thought to be due to the formation of a difficultly soluble complex of iron with antabuse. The reappearance of symptoms and their subsequent abolition by further injections is not entirely clear, though Jokivartio (92) postulates that the entire quantity of iron is immediately available to combine with antabuse when injected after alcohol is taken, while if injected some time before alcohol ingestion, the iron may become bound in the organism in some different manner before it reaches the antabuse.

The antidotal effect of iron on the TETD-alcohol reaction was further investigated by Christensen (93), who showed through manometric recording of blood pressure in dogs that an increased acetaldehyde level in the blood and doses of 1, 1-epinephrine produced similar effects. The sympathomimetic action of acetaldehyde could be verified by reversal with an adrenergic blocking agent.

The action of both TETD acetaldehyde and 1, 1-epinephrine is to prolong the vasodilating phase, and it is assumed that the action of TETD is to alter the response of specific sympathomimetic receptor cells to acetaldehyde or 1-epinephrine. Intravenous injection of iron salts reverses the phase of prolonged blood pressure fall in the absence of elevated blood acetaldehyde levels. This is explained by the assumption that TETD

combines with the iron, thus eliminating its action on specific vasodilating receptor cells of the sympathetic system, without affecting inhibitory action of TETD on the oxidation of acetaldehyde.

Ferrous chloride and ascorbic acid, either alone or in combination, do not affect the concentration of acetaldehyde in the blood. This indicates that the rapid disappearance of the toxic effects caused by TETD and alcohol as mediated by the subsequent administration of ferrous chloride, is not due to the concomitant disappearance of acetaldehyde. One to two grams of ascorbic acid administered intravenously has no effect on acetaldehyde concentration in the blood during a TETD reaction. It has been reported, however, to have a favorable effect on subjective symptoms such as headache, palpitation, apprehension and weakness.

Administration of 1% methylene blue intravenously in amounts of 1 to 20 cc had no effect on the TETD reaction as determined by changes in cardiac rate, blood pressure, conjunctival injection, or flushing. It may be concluded that if xanthine oxidase is inhibited by TETD, either methylene blue in the given dose is unable to overcome the inhibition, or xanthine oxidase is not of major importance in acetaldehyde metabolism in vivo.

A non-specific reversal of the TETD reaction by vitamins has been demonstrated by Greenberg (94), as measured by decreases in the blood acetaldehyde. Nicotinamide was active at 1.64×10^{-4} M but not at 1.64×10^{-5} M. Other vitamins, pyridoxine, riboflavin, thiamine, folic acid and ascorbic acid, produced the same picture in rats.

Oxygen inhalation abolishes the hyperventilation in TETD reactions, suggesting that the response is due to irritation of the chemoreceptors in the carotid body. Nicotinamide and adenine have been reported by Lecoq (95) to prevent a severe reaction provoked by alcohol in patients treated with TETD.

A number of procedures have been instituted in an attempt to antagonize the depressant effects of alcohol and to hasten the return to normal behavior in intoxicated persons. Analeptics are moderately effective as regards the grosser aspects of drunkenness, providing the degree of depression is not great. They are ineffectual or much less effective in restoring the impairment in coordination, judgment and altered behavior. Amphetamine, caffeine, pentylenetetrazol, and ephedrine all may restore an unconscious patient to consciousness; however, unless the doses are repeated there is generally a rapid relapse. In carefully controlled studies dexedrine and caffeine had no effect on the impairment in balance, hand steadiness, flicker fusion or EEG tracings produced by alcohol intoxication, and these agents are not practical antagonists of the central depressant effect of ethyl alcohol in man.

Fructose has been studied extensively and it is reputed to both increase the rate of disappearance of alcohol from the blood stream and to restore impaired cerebral metabolism. Berg (96), evaluating the possible sobering effect of levulose, concluded that while the depression in skill secondary to alcohol ingestion could be reversed in part and a subjective feeling of sobering up could be elicited, clinical effects of levulose were unpleasant and in spite of a lowering of the blood alcohol curve and a decline in degree of intoxication, the compound should not be recommended as a sobering up agent. The dosage needed to produce results has very unpleasant effects, the sobering up effect is of short duration, and the lowering of the blood alcohol concentration is not sufficient to warrant the dismissal of the patient.

Neither alcoholic patients nor normal male subjects administered alcohol in doses of between .5 and 2 gm/kg showed any improvement in the performance coordination or dexterity tests after intravenous injection of 0.5 to 2.0 gm of pyridoxine hydrochloride. The effect of this substance on alcohol intoxication is minimal.

The question of tolerance to alcohol is discussed in the section on the effects of alcohol on the nervous system.

IV

EFFECTS ON THE NERVOUS SYSTEM

Men long ago learned to drink alcoholic beverages as a bracer to cloud, and therefore mitigate, anticipated stresses or impending experiences, and as a hypnotic to disorganize or blunt neurotic anxiety. No drug has been used to an equivalent extent on Western civilization. The qualitative effect of alcohol on the central nervous system is a matter of wide human experience. Quantitative assessment, on the other hand, is an extremely difficult procedure, not well performed even by experimentalists, and difficult of interpretation. While the literature abounds with such reports, they are largely fragmentary, contain too few subjects, lack adequate controls, and are poorly designed. Carpenter (97) reviewed the effects of alcohol on some psychological processes and pointed out that as regards reaction time, little has been contributed since the elaborate analysis of the subject made in 1940 by Jellinek and McFarland (98); that as regards the sensory phenomena, most of the experiments represent shallow excursions into the field and are relatively uninspired; and with regard to the intellectual functions, present experiments are not satisfactory by virtue of the very nature and difficulty of assessment of intellectual functions.

In measuring responses to alcohol requiring even simple tests, there is a complex change of sensory perception, mental recognition of a stimulus, and choice of appropriate action, all of which may respond to alcohol in different ways, so that the end result is a summation of these effects. It is not surprising, therefore, that studies of even such a simple things as reaction time have given varied and contradictory results.

Attempts to show a depressant effect of small quantities of alcohol on simple reaction time generally are negative. Instruments have been designed which incorporate an element of memory into the complex reaction time test. Even with untrained subjects there is a small but highly significant slowing of response in the presence of mildly depressant doses.

Goldberg (99) has described, in a classical work, quantitative studies in man relating to alcohol tolerance, impairment of sensory, motor and psychological functions. Sensory functions are generally influenced at lower concentrations of alcohol in the blood, and physiological functions at higher concentrations. Departure from normal values are greatest in the motor functions. The differences between the appearance and the disappearance thresholds, that is, the alcohol concentration in the blood at which impairment appears or disappears, varies according to the type of function tested. For sensory functions the thresholds coincide. For motor functions the disappearance threshold is higher than the appearance threshold, and for psychological functions the disappearance threshold is still higher.

Behavior

Patterns of altered behavior produced by alcohol in animals have been examined by a number of experimental psychologists with some interesting results. Anxiety, as measured by the response of a trained rat to a light warning it of impending shock, is significantly reduced by alcohol. The drugs meprobamate, chlorpromazine and pentobarbital all significantly potentiate the reducing effect of alcohol on anxiety. Discrimination, as assessed by the correctness of the rat's response, is also significantly reduced by alcohol and potentiated by the drugs meprobamate, phenaglycodol, chlorpromazine and pentobarbital. Inability to respond, as measured by the rat remaining in the shock area, is similarly influenced by alcohol and potentiated by the other drugs in combination. The three separate entities of discrimination, anxiety, and inability to respond, are affected by various central nervous system depressants to different degrees, and are potentiated differently.

Conger (100) studied the effect of alcohol on rats in a simple "approach-avoidance" conflict situation. Alcohol was found to abolish the avoidance conflict. Data is presented which indicates that this was due to a weakening of the fear-based avoidance response. Rats trained to depress levers in order to obtain water showed diminution of this ability following administration of barbiturates. Simultaneous administration of barbiturates and ethyl alcohol blocked the effect, and performance returned to normal. In explanation it has been suggested that the alcohol might alter the rate of absorption of the barbiturate or compete with it at the neural site of barbiturate action. Due to the small number of animals Carlton (101) used in the experiment, this may merely be random variation.

Rats trained to escape from a compartment where they experienced electric shock, the strength of escape response being used as a measure of fear or its extinction, exhibited a reduction in the strength of the escape response after alcohol, though they moved about freely. Rats trained to depress a bar to avoid electric shock spent a mean time in pressing the bar of 9.38 seconds after alcohol, in comparison with their control value of 66.34 seconds, thus confirming the fear-reducing effect of alcohol. When retested 72 hours later, a similar effect of decreased anxiety was noted, even though the physiological effects of alcohol had disappeared.

Rats stressed by being forced to swim with a weight attached to the tail appear less intoxicated than unstressed animals with corresponding blood alcohol levels, when tested by the tilted plane method. Blood alcohol levels are lower in the stressed than in the unstressed animals when alcohol is administered orally, but blood alcohol levels are identical after intraperitoneal injection. Rats already intoxicated can suddenly recover when subjected to swimming stress. However, the recovery is only temporary.

Laboratory animals trained to avoid other unpleasant stimuli show a reduction in the response to the primary non-painful stimuli with the newer psychotherapeutic agents. This again is interpreted as a measure of reduction of anxiety of the animal. When multiple choices of escape are introduced, the factor of discrimination is added to the test situation. Tested in this manner, meprobamate, phenaglycodol and alcohol each decrease anxiety, discrimination and the ability to respond. Anxiety is further reduced when meprobamate, chlorpromazine and pentobarbital are combined with alcohol. Loss of discrimination caused by alcohol is potentiated by inclusion of meprobamate, chlorpromazine, phenaglycodol and pentobarbital. The complete inability to respond as induced by alcohol is also potentiated by these drugs. Alcohol has been demonstrated experimentally to inhibit or diminish conflicting drives, and its ingestion will cause test animals to disregard a frightening blast of air in order to obtain food. Further, prolonged alcohol consumption of 5 to 10% ethyl alcohol up to a

period of five months has no effect on the acquisition or extinction of a learned pressing response using food as a reward. Utilizing a battery of tests of motor function, such as righting reflex, swimming time from point to point, gait, behavior and equilibrium, the regression of performance in rats as related to alcohol dosage does not deviate significantly from linearity. A correlation is found between impairment of performance and blood alcohol concentration.

A crucial problem as regards the effect of alcohol on behavior is: why does the same blood alcohol level affect one person one way and another similar person another way. In general the proportion of negative reactions indicating aggression, antagonism, disagreement and the like, increase with drinking. The position of the individual in the group seems to have an important effect on the increased proportion of negative reaction in test situations. Central persons increase the proportion of negative reactions, and isolates do not. Individuals with a relatively permissive attitude towards aggression, while under the effect of alcohol tend to increase the proportion of negative reactions more than others. The norms of the individuals therefore seem to have an important bearing on their behavior while under the effects of alcohol. It is observed by a number of investigators that alterations in behavior at a given blood alcohol concentration reached rapidly are greater than when reached slowly, and the individual appears to be less intoxicated at a given blood concentration during the decline in the alcohol level after the peak has passed, than during the early phase of rising blood alcohol level.

Comparison of the behavior of those suffering from alcoholism and opiate drug addiction indicates interesting differences. The normal behavior pattern of drinking is different from that involved in taking opiates. Commencing with a few social drinks there is a rapid effect on judgment and inhibitions, with motor incoordination and failure of insight as the blood level of alcohol rises. Finally slovenliness, loss of control, anesthesia, stupor and even coma occur. In contrast to this, while the narcotic addict may experience transitory nausea, there is a period of maximal appreciation of the subtle effects of the drug, including the feeling of bodily warmth, lethargy, somnolence, relaxation and comfortable detachment. Following the period of maximal appreciation of the effects of the drug, there is a gradual return to the pre-drug state, in which the user returns to his normal activities but maintains to a lesser degree the comfort, detachment and loss of tension which he experienced the first hour or two after taking the proper amount of the drug. The confirmed alcoholic, while normally wishing to become convivial and relaxed, progresses to the point of total drunkenness, the most striking feature thus being that his expressed wish is usually disparate with what he ultimately achieves. The addict on the other hand rarely desires and rarely achieves unconsciousness or oblivion

in the late stages of intoxication. Further, while under the influence of the drug he can carry out normal trades without apparent disturbance, and maintain a reasonable degree of motor coordination. The alcoholic frequently develops aggressive social behavior and becomes involved in inappropriate social relations. Except when driven to crime in order to pay the cost of maintaining his habit, the opium addict is comfortable and functions well socially as long as he receives large enough doses of the drug to stave off his abstinence syndrome. The chronic alcoholic, on the other hand, cannot function normally as long as he maintains his intoxicating state. Thus the chronic alcoholic suffers in his intoxication while the opium addict suffers primarily in its abstinence.

Reaction Time and Coordination

Impairment in coordination has been demonstrated in subjects whose skills have been measured repeatedly during the absorptive as well as eliminating phase of alcoholization. Bschor (102) demonstrated that the threshold of impairment might be as low as .02% during ascent of the curve and disappear at .12% during the descent of the curve. He also noted that at a concentration of .14%, performance was impaired to the extent of 94% in single subjects during the rising level, and to only 14% when it was falling. The explanation of this event in terms other than "compensation of the organism" as advanced by the author, may be that a greater concentration occurs in the brain during the rising phase than is reflected by venous blood samples, and that the cells respond more forcefully to a given alcohol concentration achieved rapidly than to the same concentration achieved gradually.

Joyce (103) evaluated the effects of ethyl alcohol on reaction time to visual and auditory stimuli, and speed and accuracy in typing. With alcohol subjects typed faster but made more errors. Subjects frequently made definite statements about their performance which indicated they assigned a better degree of skill than was obtained by measurement.

Mueller (104) reported that drawing tests and reaction time are adversely affected by alcohol in 80% of subjects at .10%, and in all subjects at .15%. The typing efficiency of five professionsl typists who had ingested .5 to 1 gm of absolute alcohol per kg of body weight, was adversely affected long before clinical signs of intoxication could be observed in the subjects. Graphologic tests comparing handwriting, the time required for writing, fine motor coordination and accuracy, show significant differences in normal male subjects following the ingestion of bourbon whiskey in amounts sufficient to reach a concentration of between .05 and .175%. Using a commercial target shooting device of the type found in amusement parks,

Newman (105, 106) found that there was a critical level of blood alcohol for each individual at which coordination began to drop significantly. Small increases above this level produced proportionately large losses of coordinative ability. These functional decrements occurred at lower levels than a diagnosis of intoxication could be made clinically.

Reaction time to optic and acoustic stimuli is impaired at levels of .08 and .1%, although for a longer period during the elimination phase than during the absorption of alcohol. Sleep, temperature and exercise have no effect on improving the performance. Alcohol increases the reaction time to simple visual stimulation, while caffeine tends to return the lengthened time toward normal values. However, the changes in simple visual reaction time are so small that there is negligible impairment at blood levels below 0.1%. On the other hand, motor tasks consisting of removing sleeves from one set of pegs and replacing them on pegs on a different board, are influenced by ingestion of as little as 45 cc of absolute alcohol as measured by the median time required to perform the task. While subjects performed less well after receiving alcohol, their learning ability as measured by increased dexterity is not impaired on subsequent sessions.

Cerebration

Alcohol appears to have a stimulant action on the central nervous system because of its depressing effect on inhibitions. Actually, alcohol depresses the higher brain centers, diminishing the feeling of responsibility and releasing more primitive functions. A variety of test situations among different test groups point to the decrease of cerebration at a certain threshold alcohol level, which differs markedly among testees, below which there is no significant impairment and above which deterioration is rapid. As regards creative ability, Froster (107) has indicated that the majority of contemporary writers feel that alcohol brings no inspiration.

The greatest disturbance in the sensory functions generally becomes manifest at a time later than the time of maximum blood alcohol levels. The greatest disturbance of motor function, on the other hand, coincides with the blood alcohol maximum. The greatest psychological disturbances generally occur earlier than blood alcohol maximums. These thresholds range from .03 to .06, being considerably higher in the heavy drinker. Sedation threshold, defined as the amount of ethyl alcohol required to produce slurred speech in testing sessions, showed a positive and significant correlation with amobarbital used in a similar fashion. Impairment in performance of certain tests,, such as sentence completion, two-handed coordination, and steadiness in tapping speed, correlated with the threshold but not with the dose of drugs used. Alcohol ingested in amounts equivalent

to a double whiskey had no significant effect on the intelligence test score as measured by Chetell 11 A tests. The average score of the test group was only 4 points lower than the average placebo score. Subjects given a battery of tests intended to measure intellectual functions and dexterity show a significant impairment in all performance scores when the blood alcohol reached a mean of .17%. In tests to determine whether intellectual function and dexterity are still impaired when alcohol had been eliminated from the blood, it was determined that brandy drinkers had no impairment, while there was occasional impairment in some of the test scores during hangover secondary to beer intoxication. These results are similar to those obtained in studies of fatigue and mental stress, and it is important to consider that the test situation itself, with prolonged hours and concomitant lack of sleep, may have been a factor.

Alcohol in small doses reduces the number of small errors but increases the number of failures in rats trained to run a maze. Acetaldehyde also produces a similar effect, though of short duration. However, when the two substances are administered together, the effect is much greater than after each drug alone. The synergistic effect with alcohol seems to persist long after the cardiovascular disturbances of acetaldehyde disappear.

Wechsler (108), in a study of the I.Q.'s as determined by the Wechsler-Bellevue Adult Scale in a series of acute alcoholics, chronic alcoholics and normal individuals, concluded that a significant deterioration of various higher mental activities occurs over a 10-year period of alcoholism, but was not diminishable after acute alcoholism alone.

When experimental subjects are given alcohol calculated to produce a concentration of .10% in the blood, varying effects upon fluency of conversation are obtained. However, the two major effects are that alcohol reduces the fluency of word production as it reduces many other functions of the organism, and reduces conformity to standards of performance. In tests of fluency with moderate degrees of restriction, ingestion of alcohol in experimental subjects relaxed their standards of conformity so that they may make higher scores than without alcohol, but these are frequently associated with error.

Nerve Transmission

Alcohol acts as a depolarizing agent for excised nerve tissues in concentrations of 9.2 to 0.46% by volume. The rate of depolarization increases rapidly with the concentration of alcohol. However, alcohol has no demonstrable direct effect upon the excitable mechanism, since the

ability of nerve fibers to conduct electrical impulses can be restored by raising their membrane potential.

Alcohol concentrations between 4 and 10% increased excitability of the nerves of frogs, while concentrations between 15 and 25% caused rapid paralysis of the nerves. Absolute ethyl alcohol injected into leg and muscle sciatic nerves of cats caused destruction of muscle tissue. Muscle regeneration occurred in seven days. No sign of axis cylinder regeneration was noted in the nerve in this time. It may be concluded that injected alcohol causes local anesthesia by nerve destruction rather than by nerve blockade.

A concentration of 1.23% alcohol increases the stimulation of the motor end plate in isolated nerve diaphragm preparation, while concentrations of 2.56% inhibit this effect. Both concentrations counteract the inhibiting effect of curare, and similarly, paralyzing concentrations of curare counteract the inhibiting effect of alcohol.

Jarnefelt (109) has postulated that alcohol interferes with the active transport of sodium across the cell membrane, causing a decrease in its rate of uptake, which also means that the process that is the energy source of this reaction, the splitting of ATP, is slowed up. This leads to the production of less ATP, and, through the mechanism of respiratory control, to a lower respiratory rate. The lower rate of sodium transport leads to a smaller difference in concentration on the two sides of the membrane, and thus to a lower membrane potential.

Alcohol injected into cruciate cortex and hypothalamus of cats at concentrations of .02% causes a central stimulation as determined by changes in the threshold value for electrical response. At higher concentrations which are depressant but not toxic, the motor responses of the cortex to electrical stimulation are depressed. In unanesthetized cats the electrical reactivity of the hypothalamus is increased by direct injection of .01% alcohol, but not materially changed by intraperitoneal administration at doses as high as 1 cc per kg.

Kalant (110) has advanced an interesting theory concerning the site of alcohol, pointing out that higher levels of the central nervous system exert selective stimulatory and inhibitory influences on synaptic transmission between neurons involved in spinal reflexes, and that the apparent change in reflexes and motor nerve conduction may reflect an effect of alcohol upon peripheral rather than central neurons. He further contends that neither biochemical nor neurophysiological evidence supports the idea that alcohol acts primarily and directly to depress the cerebral cortex. He believes it more likely that alcohol acts on some regulatory structure, probably the

reticular formation of the brain stem, midbrain and thalamus, which modifies activity of the cerebral cortex as well as that of the peripheral neurons in the spinal and brain stem reflexes. Intoxication from alcohol may reflect, therefore, elimination of organized patterns of cortical electrical activity and increased excitability of cortical cells, resulting from mild depression of the reticular activating system with release of the cortex from selective control and inhibition.

Wallgren (111) sought to establish a relationship between ethyl alcohol and the acetylcholine system in the cortex. In vivo, rats given lipid-soluble thioacetylcholine analogs in addition to alcohol had a profound degree of intoxication as measured by tilted plane tests. In vitro, the lipid-insoluble substances acetylcholine, curare, deca- and hexamethonium were inactive in arresting unstimulated glucose metabolism in brain tissue respiration. The thioacetylcholine analog, a detergent, and ethyl alcohol, however, all caused a transient increase in respiration. Atropine and ethyl alcohol further diminished or abolished the response to electrical stimulation. The inference of this work is that acetylcholine is involved in the response of brain slices to electrical stimulation, and that ethyl alcohol may depress such responses to stimulation by a non-specific action on this system.

In initial stages of light and medium intoxication, motor chronaxie is shortened, while the chronaxies of antagonistic muscles are equalized or show a reversal. In sleep induced by medium alcohol intoxication, the chronaxie is lengthened, but not more than normal sleep. In narcosis induced by alcohol, there is marked increase in the chronaxie. While alcohol reduces the chronaxie as measured in rats, in the presence of apomorphine or TETD the chronaxies rise higher and do not return to normal as rapidly. Nerve chronaxies are lowered in rats receiving 5 to 10 gm/kg of absolute alcohol after two or three days, and level off at a lower plateau. Muscle chronaxies rise on the 7th to 10th day. Glucose and lactose administered to these chronically intoxicated rats had slight effect on chronaxies, and vitamins B_1 and B_2 had no effect at all.

Alcohol has a biphasic effect on the excitability of the central nervous system as determined by the susceptibility of mice to experimental convulsions. It raises the convulsive threshold of treated mice 3.57 times that of controls. The maximum anticonvulsant activity occurs about 30 minutes after administration and then assumes a gradual decline, being lower than the controls 12 hours after administration. It apparently prevents full seizure spread and elevates the threshold. Interpolating these results to man, one would expect seizure susceptibility in the sobering up phase of intoxication.

The modification by alcohol of maximal electrical shock seizures in animals is similar to that produced by clinically effective antiepileptic agents, but with a lower protective index. The threshold is raised 20 to 100%, depending on the dose of alcohol administered. Chronic administration of alcohol continues to elevate the threshold and serves in a protective capacity over a period of two weeks. However, on cessation of administration, animals become hyperexcitable with a lowering of the threshold level, resulting in deaths from levels of stimulus which did not produce a lethal effect while the alcohol was being administered. This transient hyperexcitability which temporarily supercedes the anticonvulsive effect of alcohol supports the view that epileptic patients should abstain from alcohol.

Rats can be rendered more susceptible to seizures by a diet deficient in available magnesium, or by a normal diet which contains 10% alcohol as the only fluid supply. A rapid decrease in serum magnesium is achieved in animals fed magnesium-deficient diets when they also receive alcohol. Cerebral cells have an increased concentration of sodium while the serum is relatively low in magnesium. Animals maintained on a 5 or 10% alcohol fluid intake for a period of 129 to 157 days showed an increase in both minimal seizure and maximal seizure thresholds. The experimenters concluded this was due to the direct depressant action on the central nervous system, but the explanation may not be sufficient, since other investigators have shown their rats developed tolerance to other motor functions after nine weeks.

Alcohol has been demonstrated to reduce the frequency with which audiogenic seizures may be produced in rats at relatively low blood levels, from .02 to .04%, and to completely abolish the response at .08% and greater. Low blood alcohol concentrations therefore diminish significantly the response of animals to stress that normally evokes grossly disturbed behavior. As these animals are still responsive to auditory stimulation and demonstrate normal exploratory activity in the testing box, it would appear that the abolition of seizures arises from either a functional lower sensitivity to stimulation, or from decreased locomotor activity. The results may be interpreted as lending support to the view that seizure behavior is facilitated by the arousal of a conflict mechanism.

Reflexes

Alcohol in doses of 1.5 to 2.0 cc/kg of body weight increases sensory threshold sensitivity, pain thresholds, and motor reactivity of conditioned reflexes; it slows respiration and the respiratory conditioned reflexes. At this dose level it has a more pronounced effect on motor conditioned reflexes than does 20 to 30 mg of amphetamine, and favors excitatory

reactions. Using a modified Romberg test, the degree of swaying in experimental subjects ingesting brandy or beer was demonstrated to be significantly increased by blood levels of .10% and above. Lower blood alcohol levels resulted in no significant increase in the swaying value as recorded by kymographs.

Alcohol produces a depression of both monosynaptic and multisynaptic reflexes in decorticate cats. The effects first appear at alcohol concentrations of .05% and are not seen with barbiturates, according to Kolmodin (112). Both anoxia achieved under diminished atmosphere at pressures of 450 mm Hg and ethyl alcohol at .5 cc/kg, decrease the normal cremasteric reflex in animals.

Cortical reactions under the influence of moderate doses of alcohol, especially as they relate to conditioned reflexes, are complex and polymorphous. At low levels of alcohol increased salivary responses occur in conditioned dogs, whereas these responses are diminished at higher doses and can be blocked entirely if the animal is habituated to alcohol.

Petrova (113) reported on both chronic and immediate effects of alcohol in dogs by means of conditioned reflex activity. The effect of alcohol is first shown by decreased inhibitory processes and later by decreased excitatory processes. Small doses of alcohol improve the conditioned reflex activity in all dogs. Sokolov (114) reports that in dogs with classically conditioned reflexes of salivation, alcohol contributes to the extinction of this reflex by two different mechanisms: first, it affects the weak links in cortical functioning without affecting the total functioning of the cortex; then, as the dose is increased, it depresses all earlier established reflexes.

Ethyl alcohol exerts an emetic action, whether administered intravenously or orally, if the concentration rises rapidly. This generally appears at a level of about .12%. Complaints of vertigo, diplopia and the occurrence of nystagmus, but not obvious deterioration of the nervous system, occur before emesis.

Goldberg (115) made quantitative measurements on the degree of alcoholic intoxication in animals by relating the blood alcohol level to the return of certain basic reflexes. The average blood alcohol in per cent at which the various signs observed returned to normal are as follows: head reflex, .302; ataxia, .25; postural nystagmus, .26. Corneal reflexes remained unaffected in all cases at subanesthetic levels.

Utilizing galvanic skin response as a measure of the reflex activity of the sympathetic nervous system, differences can be shown between

ingestion of a wine and aqueous solution containing the same quantity of alcohol. The difference is attributed to the emotion-provoking effect of unpleasant taste, and possibly the disagreeable gastric action of the alcohol solution. Amounts of alcoholic beverage considerably less than those commonly observed to cause intoxicated behavior can be shown to reduce emotional tension as measured by skin conductance to a significant degree. The response is negatively related to pre-drinking conductance levels, indicating that some of the subject's characteristic responsiveness remains after the ingestion of alcoholic beverages. In addition, it is negatively related to the conductance level of the subject at the time of measurement. Carpenter (116), extrapolating from this data, reaches the conclusion that reaction to stimulus requires more time under the influence of alcoholic beverages, but that this is compensated for by greater intensity of response. At a blood level of .05% there is a reduction of "emotional" responsiveness and alteration of "emotional" level, while simple or well-practiced skills remain intact. It appears that after moderate amounts of alcoholic beverages the drinker is less excitable, if only moderately less excited.

Electroencephalographic Changes

Neurologists do not agree upon the significance of changes which occur in mild alcoholic intoxication and in chronic alcoholics, if these changes do occur. This may reflect the highly subjective aspects of the interpretation of the electroencephalographic readings which now exist.

In some individuals electrical seizure discharges may be activated following the ingestion of alcohol, and abnormal waves increase in frequency. A slowing of the overall rhythm occurs with increasing brain alcohol levels. In conditioned dogs small amounts of alcohol are reported to result in hyper-excitability which is accompanied by increased electrical frequency in the EEG. Alcohol increases the reaction time to a light stimulus by 30% as measured by EEG's of animals kept in darkness. The initial response to alcohol, as measured by EEG's, is activation of the alpha waves. As blood alcohol level increases, the waves become sluggish. This is more pronounced during the rise than the decline of the blood alcohol curve. Subjective feelings in human subjects correspond well with the EEG tracings.

The EEG's of unrestrained or curarized cats with implanted brain electrodes vary with the level of alcohol. The general effect is a reduction of frequency and a decrease in amplitude. At low levels of alcoholization, that is, .02 to .04%, the EEG is characterized by spindle, slow wave patterns consistent with a narcotic action. At levels over .30%, generalized

irregular delta activity predominates and parallels the comatose state of intoxication. The electrical activity of the thalamus and the caudate nucleus is similarly altered, though the striatum seems to be less affected.

There seems to be little difference between chronic alcoholics and the normal population on the basis of the percentage showing alpha activity, or on the basis of the average amplitude of this activity. In contrast, however, there is a striking difference between the two groups when the alpha indices and the degree of amplitude modulation are compared. The average alpha index of normal subjects is 72% and that of chronic alcoholics about 46%. Good amplitude modulation is more frequent in the controls, and poor amplitude modulation is much more frequent in alcoholics. It has been suggested that the poor alpha type of record in alcoholics may be the result of a cerebral condition predisposing to alcoholism, and not the result of alcoholism itself. A testing of this hypothesis would require long-term follow-up studies of presumably normal controls to determine whether those showing low alpha indices in their EEG's are more prone to become alcoholics.

In serial EEG's obtained over a period of 40 days, during which chronic alcoholics maintained blood levels of approximately .2% of alcohol, there rapidly appeared a diffuse slowing which persisted during the entire intoxication period. On withdrawal of alcohol, no particular EEG pattern was associated with the mental changes appearing during the abstinence syndrome. Records taken during withdrawal were considerably obscured by muscle artifacts, though low voltage fast activity appeared more prominent than in the control records. Transient mild but definite dysrhythmias were noted.

The degree of change in the EEG following a simulated exposure to 16,000 feet partial pressure is similar to that seen during the period of development of the first symptoms of experimentally induced alcohol intoxication and during reduction of blood sugar to a 50 mg% level. The degree of change becomes considerably greater during severe intoxication. Overt behavior is markedly different, however, from that of the alcoholic intoxication state, the former being generally euphoric or aggressive, while during anoxia it is essentially normal, and during hypoglycemia relatively anxious. The behavior pattern in any of these situations varies considerably, regardless of the exciting agent, and is related to previous personality structure and the social and psychologic implications of the experimental procedure.

It has been suggested that EEG disturbances in alcoholics may be related to inhibition of cholinesterase, a substance which is electrogenic on lipoid surfaces. Experimentally alcohol inhibits decomposition of

acetylcholine by brain esterases in vitro in concentrations of .05 to .10%. Barnes (117) has interpreted this as indicating an increase in the total quantity of acetylcholine with manifest increased cerebral activity.

EEG records of a male alcoholic patient, age 31, with a history of convulsions on previous withdrawal of alcohol, showed no abnormal patterns after tranquilizers or alcohol. However, he did become hostile at blood levels between .11 and .16%, even in the presence of tranquilizers.

Neuropathy

A basic nutritional deficiency is the basis of alcohol neuropathy, vitamin B_1 deficiency being the dominant one. Direct causation through alcohol has been abandoned in view of the identity and similarity of alcoholic neuropathy to beriberi, the inability to produce the disease in alcoholized animals, the observation that adequately nourished alcoholics do not develop it, and that vitamin B_1 deficient diets can produce experimentally, characteristic lesions in peripheral nerves, as well as clinical manifestations of the disease.

A positive Babinski sign occurs in only 8% of adult patients hospitalized for alcoholism, while gross tremor, especially of the upper extremities, is observed in 43%. The extreme rarity of the Babinski sign has suggested that lesions of the coritcospinal tract are rarely produced by alcoholism.

The prime non-opthalmological abnormalities of Wernicke's disease are: ataxia of gait, confusional states of the Korsakoff variety, and polyneuropathy. Wernicke's disease has been recognized as a complication of chronic alcoholism, and alcohol per se has been presumed to be responsible. However, evidence has been produced recently that the disease should be considered primarily an expression of a nutritional deficiency state, and that alcohol is implicated only secondarily because of its effect on nutrition. Severe emaciation, pleural effusion, cardiac irregularities, peripheral neuropathy, and skin lesions were present in all patients. These conditions are associated with vitamin B deficiency. Inebriety, although contributing to the deficiency state in 43% of the group, was not a primary factor in all. Blood pyruvate levels in such persons are elevated, averaging 2.17 mg/cc, in comparison with the normal subject's 0.98 mg/cc. The blood level of pyruvate in both normal patients and those with Wernicke's disease, rises after administration of test doses of dextrose, but to a much higher degree in the latter group.

In an examination of another series of cases which showed predominantly parenchymatous cortical cerebellar atrophy, prolonged ingestion of

alcohol was the only demonstrable etiological factor in the majority of cases. While it may not be the only agent responsible for this condition, since it is current opinion that the majority of cases are of toxic origin, a careful history should be elicited in all cases. The argument against the alcoholic etiology of primary cerebellar atrophy is the supposed scarcity of this condition among alcoholics. However, it is believed the condition may frequently be misdiagnosed as peripheral neuropathy, multiple sclerosis or cerebral arteriosclerosis.

Pupillary anomalies, as indicated by sluggishness to light, fixation to light, irregularity in shape, and inequality between the pupils, were found in 44% of a group of over 600 chronic alcoholics admitted to a hospital for psychopaths. Polyneuritis was 2.5 times more frequent and generally more severe in the chronic alcoholics with psychosis, as compared to those without psychoses. Gordon (118) reported on atypical neurological syndromes of alcoholic states, describing four cases of alcoholic psychoses with pyramidal symptoms. He indicated that these were associated with marked polyneuritic symptoms, that they did not constitute a factor of prognostic seriousness, that they tended to subside under adequate therapy with thiamine.

Litvak (119) describes a latent pain syndrome elicited by palpation of muscles in certain regions of the body in cases of alcoholism. It was present in approximately 97% of alcoholics, principally on the right side of the body. The pain, which is stable and diffuse, disappears only slowly.

Under certain experimental conditions ethyl alcohol is demonstrated to have an effect on the permeability of cerebral blood vessels. This follows injection into the carotid artery, local application to pial vessels, or perfusion of cerebral vessels. The disturbance is noted only in high concentrations, far above those which could be obtained physiologically, and it is improbable that alcoholic intoxication could cause blood-brain barrier damage.

Neuropathy in the form of central necrosis of the corpus callosum was found in a 61-year old painter who had drunk "dago red" wine for many years. A reduction of food intake and therefore vitamins, as well as some peculiarity of the wine, were thought to be responsible for this peculiar lesion, the third of its kind reported in the United States.

A hemianesthesia of the external lateral part of the sclera of the eye is described in chronic alcoholics. The test is recommended as objective identification of chronic alcoholics. The basis for the sign is that the lateral and medial parts of the sclera are separately innervated, and the lachrymal glands secrete alcohol into the lateral portion only.

A comparison made of the total protein in the cerebral spinal fluid of 640 chronic alcoholic patients with psychoses, 180 chronic alcoholics without psychoses, and 160 psychotic patients without alcoholism, all of whom had negative Wassermanns, indicated no significant difference in the prevalence of abnormal protein values, which averaged about 20% in all groups.

Flinck (120, 121) reported that alcoholic patients with a tremor have a decrease in magnesium concentration of their blood, roughly correlating with the severity of sumptoms, the mean concentration being 1.46 mEq/liter in mild to moderate symptoms, and as low as .87 mEq/liter in severely ill patients. Intramuscular injection of 50% magnesium solution produces good results with an abolition of the involuntary muscle activity. Readministration is generally required to avoid relapse.

Mental Disease and Alterations in Behavior

Based on a clinical picture and etiology, alcoholic mental disorders are classified into the following eight categories: acute alcoholism, pathological intoxication, delirium tremens, Korsakoff's psychosis, acute alcoholic hallucinosis, alcoholic paranoia condition, chronic alcoholic deterioration, alcoholic epilepsy, and dipsomania. In this review we are concerned primarily with the alterations associated with acute intoxication, alcohol addiction, and the toxic psychotic manifestations.

Examination of patients with a diagnosis of psychosis due to drugs or other exogenous toxins shows a similarity in the social background, physical and psychological makeup of both drug and alcoholic addicts. Social maladjustment and inadequacy is a basic finding in both types. The reasons generally assigned by the patients using either drugs or alcohol are identical, and are related to the desire to escape from reality. Drug psychoses are relatively unimportant in numbers, compared to alcoholic psychoses.

Mendelson (122) has documented addiction to non-ethyl alcohol and other hypnotic compounds, indicating that such addiction can last up to 40 years. Most addicting drugs are primarily either depressants or stimulants of the nervous system. The former are taken to produce contentment and to release psychic controls on behavior, permitting regression to more infantile type of behavior. The latter are taken principally to heighten enjoyment or to produce distortions of sensation. Drugs may also be taken to express hostility against society. Continued abuse of drugs is always due to serious personality difficulties. The psychological reason for continuing such drugs as the barbiturates and alcohol is reinforced by the development of altered body states which necessitate continued use of the drug to prevent the appearance of an abstinence syndrome. On the

interruption of continuous drinking, distressing withdrawal symptoms occur, provoking the alcoholic to seek relief by the use of more alcohol. During a period of abstinence one observes clinically the building up of psychological tensions which provokes a pathologic desire for alcohol as a means of relieving this tension. In such a condition an individual may be said to be psychologically dependent on alcohol. A physio-pathologic condition cannot be discarded as one of the factors which may lead to resumption of drinking after days or weeks of abstinence.

In a study of the etiology of "rum fits" in delirium tremens, the group at the U. S. Narcotics Hospital, U. S. Public Health Service, Lexington, Kentucky, carried out an experiment with former morphine addicts who were given alcohol on a daily basis and in sufficient quantity to result in continuing and prolonged intoxication. Six of the subjects drank for from 48 to 87 days, and following abrupt withdrawal of alcohol, all developed tremors, marked weakness, nausea, vomiting, diarrhea, hyperreflexia, fever, and hypertension. Two had seizures, three had frank delirium, two had transitory visual or auditory hallucinations, or both. Only one escaped both convulsions and hallucinations. This occurred despite ingestion of adequate diet and multiple vitamin supplements throughout the period of intoxication and withdrawal period. The mechanisms responsible for the appearance of these symptoms on withdrawal are completely unknown. The data strongly support the thesis that withdrawal of alcohol does precipitate a characteristic train of symptoms including convulsion and delirium. On the basis of this, it must be considered an addicting drug.

In contrast to addiction to alcohol, addiction to other hypnotics, analgesics and anesthetics is less frequently encountered in medical literature. The polytoxicomaniac, however, will switch from one drug to another, according to availability. There is a reported an increasing abuse of and dependence on the barbiturate class and in tranquilizers among certain persons.

Since the symptoms of intoxication with barbiturates resemble those with alcohol and since tremor, convulsions and delirium follow withdrawal of either drug from chronically intoxicated persons, it has been postulated that chronic intoxication with barbiturates may be equivalent psychopathophysiologically to chronic intoxication with alcohol. The major symptoms of abstinence, convulsions and delirium, due to abrupt withdrawal of barbiturates, are significantly reduced by the substitution of alcohol. Likewise the incidence of very minor symptoms of abstinence, anxiety, insomnia, tremor, anorexia, and vomiting decrease. However, sudden discontinuance of the alcohol may reintroduce the symptoms of withdrawal. It appears that in a portion of these patients alcohol is not a complete substitute for barbiturates.

Delirium from alcohol is a syndrome in which basic physiological symptoms of disturbance occur in the level of consciousness. It is not necessarily manifested in excitement or increased motor activity. In fact, more frequently it manifests itself in various degrees of stupor and somnolence. Essential symptomatology lies in a decreased ability to distinguish between fantasy and reality. Individual differences in the degree of disturbance of the motor behavior are based on the personality structure.

The distinguishing feature in these toxic deliriums is that the unfamiliar is mistaken for the familiar, with a reduction to a more autonomic condition. There is a harmonious dissolution of function; the higher, more complex, less organized functions are put out of commission and the lower, better organized, older and less complex functions take over. There is no realization that disorientation is present.

Acute alcoholic furor is a pathological reaction to alcohol manifest by diffuse aggressive psychomotor outbursts and reduced contact with the environment. While an otherwise rare condition, it has been commonly observed in the field of military operations. The onset is acute following the period of drinking, and sometimes only small quantities of alcohol have been imbibed. There is usually complete amnesia for the event, which can be terminated by natural or drug-induced sleep.

Analysis of the mental defect in chronic Korsakoff's psychosis by means of the conditioned reflex method, has demonstrated that retention of memory is badly disturbed with the presence of an essentially intact sensorium, that formal thinking disorders exist, and that experimental data involving the patient presents a greater difficulty than more impersonal data, whether old or new.

Special Senses

Alcohol affects various aspects of vision, voluntary convergence being changed at blood levels above .03% and becoming progressively impaired as the alcohol level rises. Binocular fusion is lost at the 633 cm range, and may eventually give rise to diplopia. No marked change in visual acuity occurs at blood levels between .05 and .15%, but fusion and convergence are markedly impaired. Some visual acuity losses occur at levels of .08 to .18%; resistance to glare decreases, as does distance judgment and binocular vision, especially at the higher concentrations. Peripheral fields are least affected.

King (123) was unable to establish any decrease in peripheral vision by alcohol levels between .06 and .22%; however, he did obtain evidence to

indicate that the time to adjust from far to near vision is reduced by .1-.2 seconds.

Goldberg (124) observed that alcohol decreases fusion frequency in test animals and man. By recording electroretinograms on isolated animal eyes bathed in alcohol, he determined that the apparent stimulation by alcohol is the result of freedom from or suppression of inhibitory impulses.

Utilizing a Haber color saturation threshold meter, a reduction in the percentage of correct responses is noted following doses of 60 cc of absolute alcohol. Since all three basic colors are affected, it is concluded that the alcohol effect is due to central impairment. In gross intoxication states there occurs a collapse of the peripheral form fields with a relative scotoma for green. Dark adaptation measured in 16 young adult males with varying drinking patterns was not influenced by the ingestion of 0.5 to 1.0 cc/kg of absolute alcohol, though transitory increases of the threshold occurred among the abstainers in the group and in some occasional drinkers, causing characteristic undulations of the curve of retinal sensitivity.

Blood alcohol levels as low as .10 give rise to esophoria, possibly because a normal inhibiting impulse is decreased by the intoxication. There is also a decrease in the motor fusion reserve and deterioration of the sensory fusion amplitude of stereopsis. This together with nystagmus is the probable explanation for dizziness in the horizontal position under the influence of alcohol. Nystagmus is reported to be the earliest eye sign produced by alcohol. It occurs as early as 15 minutes after alcohol ingestion and is generally accompanied by an increase in reaction time. Positional nystagmus is seen in most severe cases of alcoholic intoxication. There is no definite numerical relationship between the alcohol values in the blood and the intensity or onset of nystagmus, but when positional nystagmus is observed, the only other commonly encountered physiological state which could be confused with it is a recent cranial trauma. In general, higher concentrations of alcohol produce high amplitudes and low frequencies, and lower concentrations produce low amplitudes and high frequencies. The threshold appears to be about .04%.

There are two phases of alcohol-induced horizontal positional alcohol nystagmus (PAN), which are separated by an intermediate period of one or two hours. PAN I lasts three to four hours and occurs during alcohol intake; PAN II lasts 5 to 15 hours and sometimes is present after alcohol has left the blood. In addition, horizontal roaming ocular movement (ROM) occurs. Administration of a new dose of alcohol during phase II has a clear-cut effect, whether the alcohol blood curve is declining or has already left the body. Depending on the amount of alcohol taken, this may be reduced

in intensity, completely abolished, or reverted to phase I. After three to four hours the situation changes again and a new phase I may again be reversed to phase II, or a depressed phase II may increase in intensity. ROM is accompanied by subjective symptoms such as tiredness, drowsiness, and sleepiness. These are fast movements from side to side, with amplitude of 10^{o} to 15^{o} average and a frequency of two to six seconds for complete revolution. Certain tranquilizers tend to increase ROM and decrease PAN, or even induce ROM where none existed before. From studies of the relative proportion of ROM and PAN, it is concluded that the combined effects of certain tranquilizers plus alcohol may potentiate a depression of the central nervous system.

In patients with unilateral labyrinthine lesions, alcohol nystagmus can be induced and added to any existing vestibular nystagmus. These findings constitute an indication of the vestibular origin of alcohol-induced nystagmus. The results of these studies have considerable implications regarding the abuse of alcohol and road or air traffic. This is particularly true since it applies in the impairment of certain central nervous system functions for a considerable period of time after all alcohol has left the body. In further investigation of this problem, preliminary data indicate other aftereffects which may last as long as 48 hours, and it is suggested that this could add serious implications with regard to flying personnel.

Certain drugs will exert an effect on positional alcohol nystagmus. Others affect the alcohol gaze nystagmus (AGN). It is the anti-emetic properties of the drug which generally influence PAN, while compounds without the anti-emetic effect are relatively ineffectual against PAN. Clinically it is important that there are drugs that can alleviate PAN without sedation. These drugs may help alleviate symptoms of hangover.

The particular effects of methyl alcohol on vision deserve comment at this time, with special reference to the etiology. Varying degrees of optic nerve damage, up to and including blindness, may result as sequelae from the ingestion of methyl alcohol. Susceptibility varies, with doses as small as one ounce causing an effect, while as much as 250 cc has been survived without permanent changes. Administration of ethyl alcohol, methanol, sodium formate and formic acid in quantities sufficient to affect the electroretinogram of rabbits and cats required, respectively, in terms of moles/kg: ethyl alcohol, .31; methanol, .31; formate, .022; formaldehyde, .0007. Since doses of methanol in the order of .005 moles per kg are sufficient to cause human blindness, and since neither ethyl alcohol nor acetaldehyde has a significant permanent effect on vision, it is apparent that the pathology in the optic nerve is secondary to conversion of methyl alcohol to formaldehyde. The difference in susceptibility to methyl alcohol

in primates and lower animals may be based on the specific differences in the rate of formaldehyde formation.

Other Senses

A rise in olfactory threshold is produced by ingestion of alcoholic concentrations of between 3 and 5%. The sensations of appetite and satiety parallel the rise and fall of the olfactory threshold. The rise produced by these concentrations is shorter than that observed after a meal. Olfactory threshold measurements can be used for determining acquired tolerance, since the olfactory threshold is highly sensitive and responds to exceedingly small doses of alcohol. Alcohol increases the taste threshold for sucrose and the gustatory threshold to the same extent as the olfactory threshold.

Little information regarding the effects on hearing has been reported in the past 20 years. At blood alcohol levels of .15% no changes occur in perception in either clinically measured or electroacoustically determined levels well above threshold values. However, there is a greater distractibility of subjects during testing.

Alcohol has definite analgesic effects and has been used by the laity for this purpose for centuries. When tested by modern procedures, such as the Wolff-Hardy apparatus, and in comparison with other analgesic substances, alcohol markedly raises the pain threshold, comparing favorably with morphine. Preceding pain does not substantially reduce this effect.

Performance

As might be expected from an agent which depresses cortical activity, alcohol decreases skill and the ability to perform specific tasks with the same alacrity, competence and safety as is possible when the individual is sober or has minimal quantities of alcohol in the brain. This reduction in performance is of special importance in three situations which involve the consumer of alcoholic beverages in relations with others. These are the driving of an automobile, the performance of his work, and the commission of a crime.

Determination of alcohol concentration in the blood of 10,000 persons involved in traffic accidents showed that in 1,300 cases the concentration was above .05%. Correlation is present between the clinical and chemical diagnosis of intoxication in 450 of these cases, and their clinical diagnosis unaccompanied by chemical diagnosis would have been totally misleading in more than half. More regarding chemical tests will be presented later.

Gruner (125) states that in Germany 35% of all traffic accidents are connected with alcohol and that drivers show an increase in "unsafety" blood levels of .07%. This degree increases 3-fold at .09 and 18-fold at .13%.

The majority of traffic accidents involving a drinking driver are concerned with the casual drinker who finds himself apprehended for drunken driving because he was irresponsible or had a misguided notion of his ability to function adequately under the influence of alcohol. The frequency of chronic alcoholics in this population is greater than that in the general population, but accounts for less than 5% of those involved in automobile accidents.

As regards the second question, it should be recalled that the effects of alcohol on the central nervous system include euphoria and a consequent lack of judgement, particularly in the appreciation of one's capabilities. Although there are individual differences with respect to degrees of impairment at different blood alcohol levels, there are wide margins of concentration within which people act in a predictable way. At concentrations of .15%, only the performance of automatic actions are done without impairment. Driving skill is affected to some extent in all persons with concentrations above .10%. A small number of people will show improvement in driving ability with quantities of less than .05%; these are generally anxious, over-cautious persons.

Buffard (126) reports little change and at times improvement in patients with blood alcohol concentrations of .05% when measurements of reaction time, memory, manual dexterity and control of gestures are recorded. Only in recording of tremors are there consistently poorer results with alcohol. However, the author concludes that even the smallest changes occurring in the driving of a motor vehicle are dangerous.

Reaction times to light and sound stimuli measured in members of the police force of the city of Sheffield with and without alcohol showed a normal mean reaction time, as recorded in hundredths of a second, of 28.6 to light and 19.9 to sound. After the ingestion of alcohol, those showing impairment but still judged as fit to drive had corresponding times of 32.15 to light and 21.31 to sound. Those judged unfit were 44.77 and 32.34. The average increase, then, in those unfit to drive was 14.28 to light and 11.97 to sound.

Experiments carried out by Bohne (127) on attention and motor coordination among experienced drinkers indicates impairment in all subjects whose blood alcohol ranged between .10 and .14%. In some there were

disturbances not only in coordination and synchronization of hand movements, but depth perception as well.

The Bowden test which measures tenacity, and reaction time tests which measure vigilance are considered adequate assessments of the type of attention required for operating a motor vehicle safely. Performance is lowered on both tests, particularly during the rise of the blood alcohol curve, in all persons in which a level of .1 or above was reached. Average impairment was 75% during the absorptive phase and 40% during the elimination phase. Translated into traffic situations, this is interpreted as indicating that the more the driver strains to observe, the less he is able to respond quickly to an unexpected stimulus.

Tests carried out to answer question three include not only simulated driving conditions in the laboratory, but measurements under road conditions. The essential difficulty with all road tests is that they cannot escape the artificiality of the test situation, that is, they are carried out during a period when the person has imbibed alcohol with the knowledge that he is to undergo scrutiny and examination. The type of performance is improved, therefore, over that which occurs under more spontaneous conditions, with the result that the data becomes somewhat biased in terms of better results than would be ordinarily obtained.

In this country the work of Heise, (128, 129), Harger (22, 130, 131, 132), Jetter (75, 133, 134, 135, 138, 136, 137), Muehlberger (139, 140), Borkenstein (141), and Newman (38, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 41, 34, 40, 44, 58, 105, 106) deserve special mention, while abroad the contribution of Goldberg (160, 161, 83, 99, 115, 162, 163, 164, 165) has been outstanding as regards the quantitation of impairment.

The accuracy of driving as measured by the Miles Motor Driving Trainer, is influenced by alcohol in test subjects, and the decrease in skill parallels the increase in blood alcohol. The mean increase in error in the accuracy of steering is 16% at a level of .08% in the blood. The amount of steering wheel movement becomes highly significant with increasing blood alcohol levels. Test subjects given a battery of psychological tests showed that performance scores in the case of extroverts is less consistent in car position and is accompanied by a larger increase in error. Extroverts show little change in speed after alcohol, while introverts generally increase speed. It is probable that the extrovert-introvert dimension of personality is related to the effects of alcohol.

Goldberg (164) tested 37 experienced drivers when they were sober and after ingestion of between 31 and 49 gm. of absolute alcohol in the form of

beer or spirits. Serving as their own controls, the subjects' driving ability was impaired by 25 to 30% after these doses, the blood alcohol concentration being .04 to .06%. At levels of .15%, all persons suffered significant loss of coordination in road driving tests as reported by Newman (153). Of importance is the finding that those who showed high skills before alcohol required generally higher blood alcohol levels before showing significant loss.

In simulated driving tests in which apparatus including conventional automobile steering wheel, brake and accelerator could be operated so as to operate simultaneously a miniature automobile passing over a moving belt, impairment of ability to perform the test could be detected in test subjects when the blood alcohol level was as low as .03%. At a blood alcohol concentration of .1%, performance had decreased to about 85% of the control level. When alcohol was given to subjects in continuing amounts during the test so as to keep their blood alcohol level at an approximately constant level, with testing carried out for three to five hours, there was no improvement at the later time periods. In other words, it was possible to demonstrate that the Mellanby phenomena could not be confirmed by objective measurement, even though the subjects frequently stated that they felt less intoxicated with the passage of time. Based on this data, Loomis (166) concludes that all subjects showed some impairment of function at blood alcohol concentrations of .05%, and current laws are regarded as being too lenient, since in most jurisdictions impairment of function is present before the legal limit of blood alcohol concentration is reached.

Four different performance tests were carried out among eight drivers habituated to alcohol, in that their profession as brewery drivers allowed them to consume not less than four liters of beer daily. Performance in 3 of the 4 tasks was definitely impaired in 7 of the 8 subjects at hand, and all subjects exhibited lower performance on the tasks involving reaction time. This was true initially after consuming the alcohol when the level was about .19%, and again on the descending portion of the curve at .13%. In all cases performance also lacked smoothness and was characterized by decreased concentration, uncoordinated movements and uneven attention. Reaction to unexpected sensations was slower and less certain. Other tests, including depth perception and vestibular nystagmus also were positive.

Road tests were conducted on ability of subjects to drive a motorcycle while they had quantities of alcohol sufficient to give blood levels up to .15%. The accuracy of driving, retention in memory, skill in handling the vehicle, and reaction time for braking, were tested. Impairment in driving efficiency was observed [illegible]l subjects above .10%, though signs of clinical intoxication were not necessarily present. Mistakes in handling

occurred at lower blood levels as well, and impaired reaction times and inability to judge speed correctly were noted at levels as low as .05%.

Utilizing highly experienced bus drivers as test subjects involved in actual driving situations, a decrease in the trustworthiness of the driver's own judgment relating to his skill was apparent at blood levels of .05%. Although reactions to alcohol varied among the drivers, performance as well as judgment deteriorated as they consumed increasing amounts of alcohol, and their tendency to overrate their ability in relationship to performance was intensified.

In a well executed and carefully controlled study to determine minimum blood alcohol levels at which impairment of ability to control and operate a motor vehicle safely becomes evident, 50 subjects were grouped according to previous drinking habits, as light, intermediate or heavy drinkers, and then after ingesting known amounts of alcohol were given practical road tests requiring operation of a car. Under these experimental conditions, impairment in driving skill of all subjects was definitely evident. In one subject, this occurred at a blood alcohol level of .03%. Signs of impairment were observed in 5 of 7 subjects whose level did not exceed .05%. Heavy drinkers showed less impairment than light drinkers at the same blood alcohol level, but 8 of 10 of the heavy drinkers exhibited signs of impairment in driving skill at blood concentrations ranging from .05 to .12%. Statistically, half of the 50 drivers tested exhibited significant impairment in driving skill at a venous blood alcohol concentration of .078%. An excellent correlation was obtained between clinical evaluation of driving impairment made by physicians as compared to the statistical determination of impairment of driving as measured by the decrease in skill. Changes in mood, behavior and emotional stability were also apparent. With respect to driving skill, these factors may be as important as motor coordination, in that most drivers after drinking forgot about smoothness of handling. These subtle changes in personality were not measured under conditions of impairment, and the experiment did not fully describe the individual's driving ability. The experiment suggests that an experienced drinking driver can compensate to some degree for the effect of alcohol on his driving performance. Regardless of his efforts, the ability to compensate fell off rapidly as the blood alcohol level rose above .1%.

Unfortunately, few tests have been conducted to assess the effects of alcohol in combination with other drugs on driving situations. One such report states that both alcohol given in amounts of 2 oz of whiskey, and meprobamate at 800 mg, adversely affected, but not significantly so, driving skills as determined in a modified auto trainer, Palmer perspiration tests, steadiness, and visual tests. Combination of alcohol and meprobamate produced no significant additions to the unfavorable effects. These

tests are open to criticism as regards the time interval between testing and ingestion of the drug, and are not in keeping with the findings of Loomis (166).

There is no doubt upon review of these data that both qualitatively and quantitatively alcohol produces changes which lead to considerable impairment of performance in both habituated and non-habituated drinkers. What would be the problem in operation of an aircraft, a device far more complicated than an automobile? Biget (167) reports that the presence of alcohol in the blood is of great importance in aviation, for in addition to alcohol's central nervous system depressing effects, it diminishes resistance to cold and to anoxemia. Flight surgeons observing military personnel who on instances have consumed alcoholic beverages prior to dangerous missions, noted reckless daring and disorganization of the highly trained skills required by modern warfare.

Horwitz (168) states in his review article of 1948 that for these reasons alcohol is contraindicated in pilots prior to flying aircraft, especially at high altitudes. While laboratory experience is limited as regards the effect of depressants on aviators the performance of 14 experienced pilots in a Link Trainer is pertinent. When tested before and after receiving varying quantities of alcohol, the pilots showed a decrease in skill at levels as low as .02% and the scores were generally lower at concentrations of .05%.

Work Performance

Intoxication is a basis for defense by the employer in his responsibilities to the employee under the Workman's Compensation Act. The state of intoxication or its absence is generally proved by the history of ingestion of alcoholic beverages, altered performance and by chemical tests of body fluids. In addition to the increased frequency of personal injury, there occurs a wastage of materials and general decreased efficiency. In analysis of 163 work histories obtained from former alcoholics, designed to elucidate a relation of industrial accident rates and problem drinking, it was learned that factors which showed low accident rates were associated with increased caution to avoid accidents, absenteeism, protection and help by fellow workers, and establishment of a routine on the job. Factors which contributed to high accident rates were tension and job mobility. A majority of persons reported fatigue, development of a spasmodic work pace and an absenteeism of three days per month after problem drinking has begun. In terms of cost to management, decreased job efficiency far outranks accidents.

Lundgren's (169) observations on the physiological changes in lumbermen who consumed average quantities of alcoholic beverages led to conclusions, based on lowering of the Snyder index by 10% and increase in the pulse rate by 13%, that alcohol weakens the physical state of a hard laborer and leads to either a smaller work output or a quicker expenditure of physical strength. Low concentrations of alcohol in the blood, up to 0.06%, had no effect on simulated work of either immediate demand or long type. Higher values up to 0.1% had a slightly deteriorating effect as regards long work measurements.

In a study of performance ability in telegraphers receiving code messages, threshold impairment commenced at approximately .02% blood alcohol level. Four bottles of beer impaired function from 56 to 72%. The threshold of intoxication, however, increased with habituation, and a higher concentration of alcohol in the blood was necessary to produce symptoms of intoxication in habituated subjects as compared with abstainers or non-habituated individuals. It is apparent that jobs requiring a high degree of skill and attentiveness are more subject to impairment than are low skill, heavy physical requirement occupations.

Tolerance

Tolerance is the ability of living matter to adapt to the presence of a foreign chemical or drug so that larger quantities are required to produce an effect similar to that originally noted. It has been noted in many species and may be due to many different types of agents. There are both laboratory experiments and clinical observations to document its occurrence with alcohol. Tolerance may rarely occur in an individual who has not had previous exposure. It is dependent on occasion to both sex and age. Wallgren (170) demonstrates sex differences in ethanol tolerance among rats of different ages; according to their ability to maintain themselves on a tilted plane, immature females were more tolerant than immature males or mature females. The tolerance is based on acute rather than chronic alcohol effects; since the blood alcohol level is the same, the tolerance is not a result of difference in metabolism of alcohol.

The degree of intoxication as measured by the ability of rats to maintain balance on a round horizontal bar was tested daily over a period of six months at varying time intervals up to three hours following administration of 50% of the lethal dose of alcohol. While initially animals were unable to maintain their balance for more than a few seconds and would not recover this ability for periods up to three hours, gradually there occurred an increase in performance, which was interpreted by the investigator, Troshina (171), to indicate both habituation and tolerance. Over successive

weeks the concentration of alcohol increased both in the stomach and in the various tissues three hours after administration, while the quantity of alcohol excreted in the urine decreased. The average blood alcohol concentration increased from .06 to .11% and the quantity unabsorbed in the gastrointestinal tract increased from 16 to 58%. There resulted, therefore, a decreased rate of absorption, a decreased rate of metabolism, and an increased performance.

Cross tolerance occurs when resistance develops to related compounds or classes of compounds. Tolerance produced in rabbits by daily administration of ethyl alcohol produces animals that are more resistant than normal animals to the depressant effects of pentobarbital, Evipal and ether, but not to Metrazol. Cross tolerance between alcohol and other central nervous system depressants is apparent. Possible mechanisms for this are: tolerance, therefore delayed absorption, decreased penetration into the central nervous system tissue, increased metabolism, and increased tissue tolerance. Newman (143) believes that the last is the only plausible explanation, though the mechanism is not explainable.

On the other hand, some psychiatrists report that an intolerance to alcohol may develop in formerly moderate or heavy drinkers not in the early stages of alcoholic psychosis, as a functional symptom to protect the patient from a growing sense of dependence on alcohol. It has been noted that a sudden loss of tolerance to alcohol may occur in persons who are on the verge of one of the diseases of alcoholism such as Korsakoff's psychosis or delirium tremens.

Laves (172) has advanced a hypothesis to explain individual differences in tolerance to alcohol based on ability to respond to stress situations. In a "stress capable" group (about 30% of the population) there is an ability of the adrenals to build corticoids, to store them and to discharge them into the blood at times of stress. These individuals are more capable of reacting in decisive situations, and are less accident prone. This may explain the occasionally observed sobering up appearance after an accident. No observations have been recorded on this phenomenon in persons whose blood alcohol concentrations have exceeded .22%.

While admitting to slight individual variations in response to alcohol, Muehlberger (139) holds that discrepancy in response between different individuals receiving the same dose of alcohol is due principally to differences in absorption and oxidation, with resulting different concentrations of alcohol in the blood. With a reasonable degree of variation, equal blood levels will be associated with equal degrees of intoxication. It is the observation of most investigators and the opinion of most clinicians that tolerance is limited and most frequently occurs at blood levels of alcohol not exceeding .10%.

V

PHYSIOLOGY

While the primary effect of alcohol is on the central nervous system, it does affect a number of other body systems, organs and tissues. Some of these effects are of secondary importance to the primary central effect.

The Body as a Whole

Data obtained on the effect of ethyl alcohol on cell survival and multiplication in tissue cultures indicate that solutions containing less than 1% alcohol are same, 2.5% alcohol inhibits multiplication of cells, while 5% alcohol completely suppresses cell migration; .02 to .5% resulted in a marked increase of survival time of cells.

Organ-body weight ratios of animals maintained on a 5 or 10% alcohol intake for a period of 129 to 157 days had smaller testes and thyroids than controls. There was a significant increase in liver weight in the group receiving 5% ethyl alcohol, but no other significant differences. No significant effects on the adrenals, or any histologic changes were noted in any organs. No significant effects occurred in growth and no mortalities occurred due to the ingestion of the two alcohol solutions. Experiments on mice have shown several differences. When a 10% ethyl alcohol solution is offered as the only source of liquid, a number of differences could be ascertained in the growth and alcoholic preference in successive generations of alcohol-raised mice. Offspring of parents fed water gained more than offspring of parents fed the 10% solution, with the exception of the second generation female mice. Offspring of alcohol-fed parents weighed less at weaning than offspring of water-fed parents. After the second generation the progeny of water-fed parents grew at a greater daily rate then progeny of alcohol-fed parents. In free choice experiments, the amount of water consumed was greater than the amount of alcohol solution. However, in all cases alcohol-raised progeny of water-fed parents consumed larger quantities of alcohol than litter-mate controls initially fed water. It would appear that alcohol per se would stimulate the voluntary consumption of alcohol by mice, and perhaps because of distinctive developing genetic patterns, more alcohol will be consumed voluntarily by mice that have been fed an alcohol solution over a period of time than those raised on water.

Other rats given free access to normal food but permitted only 8, 16 or 24% alcohol solutions in place of water, maintained their normal weight, but food intake diminished as the amount of alcohol ingestion increased. Preliminary studies on human subjects indicate that the taste threshold for

alcohol is about 2%, in contrast to rats who do not choose alcohol solutions above 6% in preference to water. Human subjects showed wide variations, some preferring solutions up to 50% alcoholic content. Further, it has been noted that rats forced to ingest alcohol as the only source of liquid intake, eat correspondingly less food, whether the alcohol be supplied as an aqueous solution of pure alcohol, beer or wine.

Water Metabolism

There is little evidence of major redistribution of electrolytes between intra- and extracellular spaces of the brain following acute alcohol intoxiation. In a study of the effect of alcohol ingestion on water and electrolyte balance, Flynn (173) demonstrated that sodium chloride and osmolarity of serum were significantly increased on days during which the patient imbibed alcohol, in comparison to days in which he ingested isocaloric amounts of dextrose in water. Hence, the extracellular space was less. However, there was no significant difference in the serum potassium levels between the test and control days. The absolute amount of total body water was significantly lower on alcohol days, and there was a significant relative dehydration on alcohol days persisting for nine hours after the start of the test. The diuretic effect of alcohol was not correlated with the rise of blood alcohol, and both the body's water compartments shared in the loss of water during diuresis. Based on this data, the contribution of dehydration to hangovers is questionable, since subjects are even more dehydrated in the morning following when headache malaise have cleared. Alcohol causes no changes in the balance other than those which can be accounted for by water loss and dehydration, and alcohol serves only to intensify and accelerate the body's normal mechanism of correcting dehydration by increased thirst and diminishing water output.

Lolli (174) demonstrated a redistribution either in rats which were starved or in fed rats given a 50% solution of alcohol. At 4 hours the extracellular fluid had increased from 33 to 44% and at 20 hours, when alcohol was no longer present, a second appreciable rise in the volume of extracellular water was observed.

Food Metabolism

Alcohol is a high calorie food and drug, requires no digestion, and poses no absorption problems. It is distributed throughout the body water and there are no effective ways of removing it except by metabolic degradation in the liver. The latter process is relatively slow, constant, and leads to complete burning of essentially all the alcohol ingested. Rate of

removal of alcohol is dependent to some extent on the concomitant carbohydrate metabolism, but is relatively independent of other factors. As a food alcohol is a highly purified diet supplying only calories, thereby precipitating several vitamin deficiencies as well as a fatty liver and eventually cirrhosis when it becomes the major energy source. In large amounts alcohol is not a good food source of calories, as are pure carbohydrate or fat. For combustion, 107 per mole of oxygen are required.

An increase in the mean lactate-pyruvate ratio was noted in persons administered alcohol by vein, at 30, 60 and 90 minutes following injection. There was also an increase in the mean beta-hydroxybutyrate-acetoacetate ratio during the corresponding times, while the organic acids in the hepatic vein rose at 60 minutes. In terms of biochemical processes involved in the oxidation of alcohol, apparently hydrogen acceptors other than the main respiratory chain of enzymes and coenzymes may be involved during the transport of a large quantity of hydrogen, so that pyruvate becomes lactate and beta-hydroxybutyrate becomes acetoacetate. Healthy men can apparently handle well large amounts of hydrogen produced in alcohol oxidation, since there are available temporary acceptors such as pyruvate. However, it is conceivable that in depleted persons alcohol may have a more deleterious effect. In the sequence of metabolism of alcohol there may be a temporary inhibiting effect on other metabolic pools.

Estimations made by LeBreton (175) indicate that among miners, the greatest consumers of alcoholic beverages in France, the caloric intake from alcohol is only 30% of the total. In the average citizen, it amounts to between 10 and 15% of the calories for men, and between 6 and 9% for women. However, in chronic alcoholics with cirrhosis, it may amount to 70%.

Alcohol is reported as having an antiketogenic effect, in that the combustion of alcohol itself has an economizing effect on fat oxidation which enables the liver to reduce its ketogenic activity. Small doses of alcohol are recommended for patients who have difficulty in ingesting ordinary food and consequently develop acidosis. Ethyl alcohol exhibits a variety of effects on fatty acid metabolism in vitro in rat liver slices. At 0.5 mM of tagged ethyl alcohol, fatty acids are labelled in a manner identical to the use of acetate as a substrate; however, at 10 mM concentration, the labelling from alcohol is 6.9 times greater than with acetate. It also increases the uptake in fat in the presence of glucose and acetate. However, ethyl alcohol has no effect on uptake from tagged palmanate, nor is there an increase of hexose monophosphate shunt of CO_2 production from glucose labelled in any position. Ethyl alcohol has no effect of fat synthesis in adipose tissue.

There is a diversity of findings relative to the effect of alcohol on the blood sugar level. Tennent (176), using rats, demonstrated that the effect on the blood sugar varied with the dose of alcohol as well as with the amount of glycogen in the liver. Small doses of alcohol caused no significant changes in blood sugar level, whether liver glycogen was high or not, while large doses of alcohol given when the liver glycogen was high caused increased blood sugar levels. Surgical anesthesia produced by sodium pentothal, cylcopropane, procaine or alcohol, resulted in a decrease of sugar tolerance for each substance in comparison with control values, and it is concluded that a general depression of carbohydrate metabolism occurs during anesthesia.

Wortis (177) reports that alcohol patients show a marked sensitivity to insulin in relatively small doses, which he ascribed to small glycogen stores. While ethyl alcohol is reported to have no effect on the utilization of carbohydrate as measured by carbohydrate tolerance in chronic alcoholics and non-alcoholics, hypoglycemia has been demonstrated to occur during the period of hangover with mean blood sugar values approximately 30% of those expected. In general, the greater the blood alcohol level the night before, the lower the sugar value. Some of the common physiological symptoms of hangover, such as thirst, headache, hunger, staggering, pallor, tremors, sweating, dizziness and nausea, may be associated with this hypoglycemia. Alcohol is a weak hypoglycemic agent in rats, as demonstrated by failure to markedly change blood glucose levels following 34 days repeated daily intravenous administration. Hypoglycemia did develop after administration of between 55 and 62 daily intoxicating doses.

Alcohol is reported to have a marked effect on the metabolism of lactose; the greater the dose of alcohol, the higher the concentration of lactose in blood and urine, regardless of whether the administration of lactose was oral or intravenous. No similar effect occurs with glucose, and only a minor effect with levulose. Alcohol probably affects the metabolism of lactose in the liver.

Determination of acetate immediately following absorption of alcohol by rabbits leads to a transient increase in volatile acids of between 15 and 25 mg%. Since this level returns to normal in some 90 minutes, although the alcohol level remains high, an adaptive mechanism, possibly due to hormone release, has been postulated.

Several studies have been done with respect to the effect of alcohol on vitamin storage and utilization, especially that of A and B. Animals maintained on a diet free of vitamin A but supplemented by known quantities of that vitamin and then administered alcohol, showed lower levels in the liver than controls did. Single administrations of alcohol do not significantly

reduce the deposit of vitamin A already present in the liver. Ethyl alcohol along with other alcohols raises the serum vitamin A level, while ethyl acetate, acetone, paraldehyde, and acetaldehyde and acetic acid do not cause a similar rise. The vitamin A appears principally in the esterified form. Feeding a 10% alcohol solution mobilizes the vitamin A content of the liver in experimental animals, whether maintained on a caseine diet or one fortified with aminoids.

The substitution of alcohol for carbohydrates has a thiamine and nicotinic acid sparing action, as indicated by increased excretion of these substances in men given an isocaloric substitution of alcohol for dietary carbohydrate. Alcohol does not deplete thiamine stores in a thiamine-deficient diet to a greater extent than is produced by dextrose. In fact, utilization of calories supplied by dextrose causes a significantly greater depletion of thiamine stores in the liver. Isocaloric substitution of alcohol for carbohydrate and fat causes a delay in the onset of thiamine deficiency symptoms in pigeons. This data is contradictory to the general assumption that alcohol metabolism increases thiamine requirement, and it may be that metabolism of alcohol and carbohydrates together requires less thiamine than the metabolism of carbohydrate alone. It is possible that the thiamine equivalent of alcohol is increased when the latter constitutes a major portion of the total daily calories.

Lowry (178) has carried out a number of experiments on rats which indicate that polyneuropathy produced by thiamine deficiency in the diet is retarded by administration of alcohol or whiskey as a source of fluid intake as contrasted to water. Average onset in the water group is 12 to 19 days and that in the alcohol group 18 to 40 days. The symptoms of polyneuropathy disappear within 24 hours after 200 or 400 μg of thiamine is administered. Lowry concludes from this data that one could not assume that alcohol increases the requirements for thiamine.

Unfortunately there is little information relative to the effects of alcoholic intoxication on the body's resistance to infection. Experimental evaluation of resistance to pneumococcal infections has indicated that rabbits maintained to a point of alcoholic stupor become markedly less resistant to infection, even when rendered immune by anti-pneumococcal serum. This apparently follows the inhibition of the vascular inflammatory response, and in the absence of capillary dilatation, leucocytic migration to the site of infection is negligible.

Differences Due to Chronic Alcoholism

Depressed chloride levels in the blood are found in chronic alcoholics due to low salt and excessive water intake, combined with excessive

chloride loss in the urine and sweat. This promotes the sensation of thirst. Instead of salt and water, the alcoholic will continue to take liquor and a stage of uncontrollable drinking may be reached. The phenomenon of craving for liquor may therefore be due sometimes to a perverted physiological craving. This, however, may be corrected by increased salt intake in the diet or parenteral administration.

The peak of blood pyruvate is higher and earlier in addicts than in non-alcoholics, suggesting that alcohol addicts have a metabolic peculiarity in their production or disappearance of pyruvate. There is no significant correlation between acetaldehyde and sugar levels in the blood of addicts.

Normal subjects, patients under stress, and patients ill from a number of disease states, have little variation in serum amino acid levels. However, in the case of delirium tremens there is a noticeable lowering of the free amino acids, which may be pathognomonic of the condition. The more serious the delirium, the greater the depletion of these essential blood elements.

Following a glucose stress test, total leucocytes, urinary sodium and an unidentified diazonium-coupling compound were found to occur at significantly higher concentrations in male alcoholics than controls. No significant differences were found in other responses to glucose stress. Glucose tolerance tests performed on 300 alcohol addicts who, at the time of the study were completely recovered from any existing acute intoxication, indicated that carbohydrate metabolism was seriously deranged in more than half. This may be attributable to disturbances of hepatic function rather than to a variety of diabetes.

Serum copper concentrations of alcoholics appear to be greater than those of control populations, whether or not either group is receiving chlorpromazine. This does not apparently reflect a higher copper intake. It is suggested that cirrhosis of the liver may be the underlying basis for the hypercupremia. Further studies of the occurrence of serum coppers in male and female ambulatory alcoholics indicate that the copper levels of both groups lay within the accepted normal ranges of 75 to 135 μg%, but that male alcoholics had a significantly higher mean than non-alcoholic control subjects.

In the study of serum iron levels in alcoholic addicts there was noted a steady decrease of the group mean values from milder conditions to the more severe ones, the lowest values being reached in delirium tremens. In mild conditions there were occasionally abnormally high values which disappeared during convalescence.

While the mechanisms and factors determining renal excretion of zinc are largely unknown, it has been established that in non-alcoholic subjects a 24-hour urine zinc content shows little variation, while alcoholics with cirrhosis of the liver do show increased amounts of zinc in the urine, as perhaps do alcoholics with no demonstrable hepatic disease. Acute alcoholic intoxication in normal subjects does not produce increased zinc excretion, nor is it increased further by the intravenous administration of 1000 cc of 5% alcohol in patients with a long history of alcohol intake.

Cerebral Metabolism

Quite adequate amounts of cocarboxylase activity are maintained in the brains of acutely intoxicated animals, though the lactate-pyruvate ratio shows a definite shift to higher values following injection of alcohol or acetaldehyde. That portion of unstimulated nerve cell respiration which is neither highly sensitive to narcotics nor capable of stimulation by potassium ions, is not affected appreciably by ethyl alcohol. At concentrations of .02 M to 0.4 M an increased rate of respiration is brought about in non-stimulated rat and guinea pig cortexes in vitro. In the presence of potassium chloride, alcohol at .02 M produces an inhibition of respiration which increases with rising concentrations of the alcohol.

Wallgren (179) measured the effect of ethanol on the respiration of rat brain cortex slices, showing that in unstimulated tissue in the presence of glucose, the addition of alcohol in the quantities of .4% increased the consumption of both oxygen and glucose, but did not affect the formation of lactic acid. In electrically stimulated tissue, ethyl alcohol caused a decrease in respiration, glucose consumption and lactic acid accumulation, while in potassium stimulated slices the effect of alcohol on respiration was less marked, but the glucose uptake and lactic acid accumulation increased.

In electrically stimulated tissue, malonate and ethyl alcohol both diminished respiration. When both inhibitors were present simultaneously, the effect of only one of them was obtained, the effect being that of the inhibitor having the greatest action in that particular concentration. At both 30° and 37° ethyl alcohol increased the respiration of unstimulated tissue, while malonate had an insignificant effect. Both compounds had a marked effect on electrically stimulated tissue at 37° and ethyl alcohol's effect, though significant, was greatly reduced at 30°. Mitochondria from adult female hooded rats at the unphysiological concentration of .4 to .8 M caused stimulation of oxygen consumption. However, in the presence of potassium chloride there was inhibition with the higher concentrations to the extent of 99%. In contrast, .2 M n-propanol, isopropanol, n-butanol, and n-pentand

slightly depressed unstimulated respiratory rate and greatly depressed the potassium stimulated rate of respiration. In the latter case this is greater than with ethanol and goes beyond the simple removal of that portion of oxygen consumption due to potassium stimulation: it goes on to inhibit resting metabolism. Brain mitochondrial respiration is relatively insensitive to concentrations of alcohol that considerably depress potassium-stimulated respiration of brain cortex slices. Quastel (180) and Beer (181) suggest that the alcohols exercise their inhibitory effect on brain cortex respiration at the brain cell membrane. This may have merit, since the effective oxygen stimulation of alcohol cannot be exhibited unless intact tissue slices are used.

Alcohol in concentrations of .02 M, .2 M, and .4 M, stimulated respiration of brain in vitro, though less so at the higher concentrations. All three concentrations inhibited stimulated respiration produced by added potassium chloride and dinitrophenol. The investigators concluded that narcotics such as ethanol, in pharmacologically active concentrations, act on the nerve cell by the suppression of oxidative events, particularly those involved in glucose and pyruvate oxidation. This would indicate that the metabolic compartment sensitive to potassium is also sensitive to alcohol, and this compartment seems to respond to dinitrophenol.

Sutherland and Burbridge (182) have shown that ethyl alcohol differs in its effect on resting metabolism of human and rat cerebral cortex. Ethyl alcohol does not affect oxygen consumption of human cortex with any variety of substrates, though it does increase the oxygen consumption of rat cortex for the majority of substrates including glucose, pyruvate, acetate and glutamate. The effect of alcohol on stimulated tissue is approximately proportional to the concentration, responses to stimulation being reduced by 50% with a .9% ethyl alcohol concentration. Ethyl alcohol acts independently of glucose concentrations, though glucose consumption of lactate acid production is changed in proportion to respiration, suggesting interference of energy-consumer systems.

Brains taken from Wistar rats one hour prior to sacrifice, which were administered alcohol sufficient to give a concentration of between 300 and 500 mg, were incubated in either Krebs-Ringer solution to which .1 M KCl had been added, or in a similar manner were incubated with a further addition of alcohol in concentrations of .125 to .5%. The alcohol slightly decreased, in a significant manner, the oxygen consumption in the latter group. However, in animals pre-treated with alcohol, further addition of alcohol to the medium did not inhibit the oxygen uptake. The customary stimulation of respiration by potassium was also less evident in the group receiving the alcohol.

Rat cortex respiring with glucose in an oxygen phase is reported to reduce respiration of unstimulated metabolism to a degree of about 21%, and to further inhibit calcium stimulated respiration to a degree of 35%.

Brain slices were made from rabbits given alcohol to reach a brain concentration of .35%. The in vitro oxygen uptake was stimulated when the brain was removed within one hour after alcohol administration. The increase was greater in grey matter than in white, and the stimulation lasted for about an hour with return to normal rate. Robertson (184) has suggested that alcohol is absorbed on the oxidizing surface, displacing the usual metabolites, but is slow to oxidize. These studies do suggest that endogenous metabolism may be affected by alcohol.

Kulonen (184) has demonstrated that ethyl alcohol in concentration of .4%, blocks the normal effect of electrical stimulation on respiration, on the synthesis of amino acids from glucose, and on the uptake of added amino acids by rat brain slices. The most consistent effect of the latter is a decreased glutamine content, Kulonen reported.

The amino acids of rat brain were determined following ethanol intoxication at various times from 20 minutes to 24 hours. In young rats an increase was observed in the content of gamma-aminobutyric acid (GABA), glutamic acid and aspartic acid, and a decrease in glutamine. The alanine, glycine, serine and taurine co ntent remained unchanged.

Utilizing radioactive carbon, Snyder (185) measured the effects of ethyl alcohol on acetyl coenzyme A formation, and demonstrated that .04 to .16% alcohol stimulated total accumulation and replaced all endogenous acetyl sources. It did not decrease acetyl formation from acetate, but replaced pyruvate, glycerine and butyrate as acetyl donors. Conversely pyruvate, glycerine and butyrate did not decrease acetyl formation from ethyl alcohol. This suggested that alcohol preempted available DPN, therefore preventing a conversion of other DPN-requiring substrates to acetyl choline coA.

Acetaldehyde causes a marked inhibition of potassium stimulated respiration of brain cortex at a concentration much smaller than that of ethyl alcohol to produce the same effect. Acetaldehyde also abolishes the increased respiration due to potassium ion at a concentration that has no observable effect on unstimulated respiration. Acetaldehyde also inhibits brain mitochondrial respiration as markedly as it inhibits brain cortex respiration. Mitochondrial inhibition observed in the presence of pyruvate is greater still in the presence of small quantities of malate. This aldehyde inhibition is abolished by the addition of DPN. Similar molar concentrations have no inhibitory effect on succinate oxidation by the mitochondria

with or without DPN. Why the addition of DPN abolished the acetaldehyde inhibition has not been established. If DPN catalyzes the removal of acetaldehyde either by oxidation or by dismutation, it should have also done so with alpha ketoglutarate or succinate, which was not the case.

The effects of acetaldehyde on alcohol as measured by the synthesis of acetocholine, acetoin, and citric acid in rat brain preparations indicate that optimal acetocholine and acetoin synthesis is obtained in the presence of acetate, pyruvate and acetaldehyde. The latter is observed to support some acetocholine and citric acid synthesis when used as the sole acetyl donor. If the acetate or pyruvate is omitted, a greater acetaldehyde utilization is obtained. Formation of these substances indicates that they are converted to a common intermediate, possibly such as acetyl coenzyme A. Alcohol has no affect on acetoin-citric acid synthesis but does increase acetocholine formation. Evidence suggests a conversion of acetaldehyde to acetocholine coenzyme A by a coenzyme A dependent reaction not requiring ATP or DPN. Data regarding the effects of alcohol using intact specimens have been obtained from both animals and man.

In 1940 Wortis (186) reported arteriovenous differences in chronic alcoholics with values higher than those obtained in normal subjects and associated with elevated arterial glucose levels. Alcohol and morphine were reported to diminish this oxygen arteriovenous differences in the brain. These cerebral blood flow studies conducted prior to 1948 could be only roughly quantitated as no interpretation of rates could be made. Studies which do not report arteriovenous differences of cerebral oxygen are meaningless.

Loman (187) reported that alcohol decreased cerebral metabolism as measured by oxygen and glucose determinations, but did not have an effect on cerebral vasodilatation. He used the technique of interruption of the outflow of blood by occlusion of carotid by means of inflated cuff and measured cerebral spinal fluid by lumbar puncture. The results of the experiment are frequently quoted. However, the results are only semi-quantitative and the procedure is poor technicologically so that it is necessary to refute the data in conclusions that are drawn.

Fazekas (188), studying three groups of patients with relation to the effects of alcohol on cerebral hemodynamics and metabolism, found no changes in any of the perimeters of blood flow or metabolism whether the subjects were given alcohol alone, chlorpromazine alone or a combination of the two. The blood alcohol levels in the study averaged .134% and chlorpromazine was given in quantity of 200 mg. His conclusion that the depression characteristics of each drug concentration employed appeared to be independent rather than synergistic or additive is open to question,

since the same patients were not used as controls for the subsequent treatment.

In a better controlled study the effects of ethyl alcohol on cerebral blood flow and metabolism were determined in two different groups of subjects. The first group was patients convalescing from a variety of medical illnesses. After initial cerebral blood flow determination they were given ethyl alcohol intravenously in 10% solution sufficient to produce visible evidences of peripheral vasodilatation. The blood levels at the time of measurement ranged between .015 and .137% with a mean of .068%. No significant differences occurred in cerebral blood flow, cerebral oxygen consumption, cerebral vascular resistance or arteriovenous oxygen differences. In a second group of subjects who were admitted to the hospital in a state of acute alcoholic intoxication and on whom cerebral vascular measurements were made, there were significantly higher rates of cerebral blood flow during intoxication, though oxygen consumption, cerebral vascular resistance and arteriovenous oxygen differences were all lower than when control measurements were carried out during the post intoxication period.

In a study of cerebral metabolism of problem drinkers under the influence of alcohol, Burbridge (189) noted an alteration in blood lactic and glutamic acids with a reverse of the normal order in the cerebral exchange of glutamic, glutamine and acetaldehyde. After alcohol these blood constituents are further increased and a hyperglycemia occurs. Blood CO_2 is reduced as is the cerebral respiratory quotient, while the cerebral glutamine exchange is normalized. After ingestion of alcohol by patients also taking chlorpromazine there is an exaggeration of abnormal behavior and a significant increase in blood alcohol but not acetaldehyde levels. Despite the fact these subjects appear normal clinically, they are abnormal biochemically and the findings suggest an explanation of the high susceptibility of alcoholics to pneumonia and intoxication.

When administered by inhalation or intravenously, ethyl alcohol had no influence on the cerebral spinal fluid pressure in dogs unless administered to a point sufficient to produce a fall of systemic blood pressure. Any direct action on cerebral blood vessels is insignificant in character.

Gursey (190) has reported a depletion of serotonin and norepinephrine in the brain stem of rabbits administered alcohol chronically over a period of seven days or acutely following intravenous infusion of 2 gm/kg. The reduction of 50% of these neurohormone levels is not confirmed by other investigators.

While reserpine in as small a dose as .2 mg/kg induces 80% depletion of norepinephrine in the brain stem and also depletes the biogenic amines serotonin, alcohol following either single or repeated administration produced no essential effect on brain amine levels even though causing deep narcosis. Cholinesterase activities of brain, liver and serum of rabbits acutely intoxicated with ethyl alcohol are about the same as normal. However, activities in alcohol-habituated rabbits are reported as being significantly lower.

Cardiovascular System

No significant effects on the circulation are caused by alcohol in other than toxic doses. Even then the depressant effect on the heart is considerably less than with the anesthetics. Following dosage of 0.5 ml/kg of alcohol, autonomic nervous system activity as measured by respiration, peripheral vasodilatation, heart rate, and finger blood volume are minimal. Stimuli administered in terms of immersion of the foot in ice water and vena-puncture gives evidence of some sympathetic stimulation in some subjects and additionally perhaps a parasympatholytic effect.

Alcohol has been observed to increase the apnea and vaso depression following sudden administration of pure oxygen to animals at blood concentrations as low as .06%.

Hexamethonium chloride causes a decrease in the hyperglycemic response to alcohol in dogs, probably on the basis of interference with the increased release of epinephrine from the adrenal medulla during severe alcoholic intoxication. After a splenectomy, alcohol still elevates hematocrit values although to a lesser degree than in intact intoxicated dogs. This may be due to decrease in plasma volume without change in the total volume of extracellular fluid. Splenic contraction as observed in the exteriorized spleen coincides with increase in plasma glucose and hematocrit and is probably again secondary to the action of epinephrine on the emptying of the blood depots in the alcohol intoxicated animal.

Blood pressures of over 25,000 alcoholics, determined at their admission to a hospital alcoholic ward for treatment and again at discharge, indicated that the average systolic pressures were similar to the average systolic pressures in the general population but that the diastolic pressures were lower than the average, though not in the hypertensive range. In addition, hypertension was much less frequent among the alcoholic patients, even at the time of admission and when emotionally upset, than in the general population. Hypotension also was much less frequent in the alcoholic patient than in the general population. The conculsion was that

alcoholics have less hypertension and less hypotension than the general population.

Patients with Laennec's cirrhosis, history of alcoholism and inadequate diet may have an increased system blood flow at rest. Investigation of resting cardiac output of chronic alcoholics without liver disorder shows no evidence of alteration. It is concluded that the higher cardiac output must therefore be due to hepatic disease or other concomitant factors rather than to alcoholism per se.

The activity of the vasomotor reflexes in the carotid body are reported to be increased with small concentrations of alcohol and inhibited at higher concentrations. In concentrations of .10 to .20%, corresponding to moderate intoxication, ethyl alcohol accelerates initial velocity of tyramine metabolism by 75% as indicated in guinea pig liver preparations. Intercarotid injections of alcohol in anesthetized cats caused increased arterial blood pressure and respiration. Denervation of the carotid sinus and aortic mechanisms abolished most of this effect. The procedure is reported also to intensify the chemical action-potentials of the sinus nerve and cause a stimulation of chemoreceptors though temporary paralysis of baroceptors.

The Funkenstein space Mecholyl response test is used as a measure of the effectiveness of various drugs in altering the central sympathetic reactivity level (CSR). In the normal basal patient at rest the systolic blood pressure which is elevated following injection of 10 mg of Mecholyl will return to normal within 10 minutes. Barbiturates and most depressant-hypnotic drugs lower the CSR regardless of its original level. That is, the level does not return to the base level during the 25 minute test period. Chronic alcoholics show no consistent change in their CSR at basal conditions or following oral ingestion of measured quantities of alcohol.

An increase in hepatic blood flow in persons in whom the hepatic vein has been catheterized is produced by intravenous administration of alcohol. This is accompanied without the impairment of dye removal by the liver or changes in cardiac output or blood pressure. The effect which is achieved at alcohol levels between .03 and .06% is possibly due to the decreased peripheral resistance in the splanchnic bed.

Rapid intravenous injection of alcohol produces changes in the coronary sinus outflow and coronary artery inflow in dogs, providing a blood concentration of .065% is reached. There is an average maximal increase of 60% in outflow and between 25 and 40% increase in inflow at this level. At high doses of alcohol resulting in levels of .11% there is an average increase of 117% in sinus outflow. Slow infusion also increases the sinus outflow by

approximately 30%. When the magnitude and duration of the alcohol's effect are compared to those of standard vasodilators such as aminophylline and papaverine, it is found that 95 mg of alcohol is equivalent to 2.5 mg of aminophylline, and .25 mg of papaverine.

Though alcohol produces peripheral vasodilatation there is no significant effect on coronary blood as indicated by tests on patients with angina. Five of 21 patients with angina pectoris who were given one ounce of whiskey 1 minute and 90 minutes prior to test were able to perform up to 27% more work than in controlled tests; 16 patients, however, showed no response. The majority of patients who took one ounce of whiskey four times a day for a week felt subjectively better but some showed decreased work output. Stearns (191) concluded that a therapeutic dose of whiskey, therefore, did not measurably shorten the duration of attacks or increase the capacity of patients for work, although it may promote an increased sense of well-being without associated objective improvement. Other exercise tests performed on patients with angina pectoris were followed by depression of the RS-T segment and flattening or inversion of the T waves. Glyceryl trinitrate, five minutes before administration of these tests, completely changed the nature of the EKG responses. In striking contrast, as much as two ounces of whiskey exerted no influence on the EKG response to standard exercise tests. Since there was an abolishment of anginal pain during the exercise test, it was concluded that alcohol did not act as a vasodilator but exerted its effect secondary to a sedative action on the central nervous system.

Alcohol has been used for years, though, without medicinal validation of its effectiveness in occlusive diseases of blood vessels. No significant body of literature is available concerning its effect on the permeability of normal vessels.

In patients with arteriosclerosis obliterans or with other vasospastic disorders the injection of intravenous alcohol fails to cause a consistent significant increase in skin temperatures. However, in spite of the lack of objective temperature increases, the majority of subjects stated that their legs felt warmer.

A study of 536 actively working people of both sexes over 40 years of age, in relation to their use of alcohol and occurrence of arteriosclerosis, indicates that there is no relationship between the use of alcoholic beverages and the incidence of this disease.

Alcohol has little effect on the extracellular distribution of Trypan blue, p-aminobenzoic acid, or sulfonamides, and there are only small

permeability changes following administration of alcohol in intoxicating doses as determined by measurements in rat brains.

No impairment in the integrity of the blood-brain barrier is demonstrated by injection of 20% solutions in the femoral veins of anesthetized cats. This is true whether alcohol is given singly or following a month's administration of alcohol solutions orally.

The intravenous injection of ethyl alcohol into the carotid arteries of dogs increases the cerebral vascular permeability as indicated by radiographic techniques following injection of radioactive albumen. The increase was appreciable at one hour, obtained a peak after two and was weak after six. No histopathological changes could be observed in the capillaries or brain tissue to account for alteration in blood vessel permeability, and transient anoxia itself as produced by interruption of the blood circulation did not parallel these effects. It is unlikely that anoxia is a major contributor to or responsible for these permeability changes.

As regards the effects on blood, it has been observed that when using human subjects in whom both the diet and fluid intake is carefully controlled, plasma, cell volume and total blood volume increased significantly in acute alcoholism as measured by the plasma volume and hematocrit readings.

In a study of the relationship of the length of the carbon chain to the primary and functional toxicity of alcohol, it was shown that human and rat leukocytes were equally susceptible to the primary toxic action of the alcohols and that this increased with molecular weight following geometric progression of 3 to an exponential power after methyl alcohol. The acute oral toxicity of the first four primary alcohols increased with increasing molecular weight while amyl, hexyl and heptyl alcohols decreased in toxicity with increased molecular weight.

Blood cell alterations as determined by a sternal puncture were reported in a group of school boys who habitually inhaled paint thinner containing ethyl and butyl alcohol. The habituation had ranged from six months to five years. Cerebral stimulation was reported as evidenced by EEG changes.

Clumping of red cells can be caused by external influences such as ether anesthesia and the ingestion of alcohol, as determined by in vivo examination of the capillaries of the conjunctival mucosa under the microscope. Electrophoresis of the blood serum and cerebral spinal fluid in patients with Korsakoff's psychosis, alcoholic hallucinosis, or delirium tremens shows a decrease in serum albumen and increase in beta and gamma globulins during acute episodes. There is also an accelerated metabolism of adrenochrome during acute episodes.

Respiration

Small quantities of alcohol have no effects on respiration as noted by the usual clinical examination of patients. The evidence presented by Hitchcock (192) suggests that a small effect can be demonstrated experimentally. However, utilizing the criteria of the rate and depth of pulmonary ventilation, the stimulating effects of CO_2 in inspired air, changes in CO_2 tension in alveolar air and the maximum duration of voluntary apnea, more recent studies have shown that small doses of alcohol have no clinical effect or importance as respiratory stimulants.

Injection of ethyl alcohol into the trachea of rabbits produces pulmonary edema and extensive pneumonia in the majority of animals, and incidental finding of a lesion which resembles human bronchiolitis obliterans. The practical significance of this relates to accidental aspiration pneumonia in the alcoholic.

Small quantities of alcohol have depressant action on the respiration of both cats and rabbits pretreated with urethane but have no further effect on respiration of animals receiving barbiturates. An appraisal of the possible potentiation with other depressants awaits well-designed studies. Dogs receiving alcohol by regulated infusion show no effects on respiratory rate or minute volume until concentrations of approximately .40% are reached. At that level and above, respiratory rate and minute volume decrease until respirations cease. A similar effect is observed with respect to the heart rate. EKG changes develop in all animals when the blood alcohol levels reach .5% or above. Changes are inconsistent, but generally involve irregularity in rate, decreased QRS voltage, increased amplitude of the T wave and ectopic systoles. If given artificial respiration, effects on heart rate and EKG changes do not appear until blood alcohol concentrations reach .88% and above. If respiration is maintained by respiratory stimulants such as Metrazol, higher concentrations of alcohol can be tolerated. This procedure, however, supplies no particular advantage over that produced by the use of artificial respiration. Persons acutely intoxicated with blood levels of .35% and above exhibit marked depression of respiration due to a depressant effect on medullary centers.

Kidney

Alcohol has no known direct toxic effect on the kidney, though the kidneys of persons surviving prolonged hypoxia episodes are occasionally temporarily damaged as occurs with other hypoxic agents.

Alcohol ingestion in normal subjects results in a diuresis characterized by decrease in osmolar and an increase in free water clearance. Where positive water balance is changed by hydration of the subject, as with an infusion of 4% fructose, alcohol does not further increase urine flow, nor does it raise either the sodium or potassium excretion. Alcohol taken during the infusion of hypertonic saline results in increased flow above that reached during maximum water diuresis and an increase in free water clearance, indicating that alcohol blocks the anti-diuretic action of hypertonic saline. However, water diuresis does not occur if the alcohol is taken after the infusion of saline, probably because an excess of circulatory anti-diuretic hormones masks the inhibitory effect of alcohol on the supraoptico-hypophyseal system.

Alcohol does not interfere with the diuretic effect of water in diabetic dogs and does not produce diuresis in dogs with diabetes insipidus at doses which invariably produce diuresis in normal dogs. The smallest effective intra-carotid administered dose is 12 mg/kg for this effect; the average intra-carotid dose is 0.2, the amount required to produce diuresis in dogs without diabetes insipidus. These findings all point to the conclusion that alcohol must interfere with the release of anti-diuretic hormone from the neural hypothesis.

The diuretic response to alcohol differs markedly in one respect from the effect of alcohol on the cerebral cortex. The latter is most effected by the rate of increase in blood alcohol concentration. The greater the rate of increase, the greater the disturbance of function at any absolute concentration. The diuretic response on the other hand is dependent mainly on the duration of the increase in blood alcohol concentration but not on the rate of increase.

Narcotic doses of alcohol induce antidiuresis in rats loaded with .2% saline to the same extent as does pentothal. This is augmented by post pituitary preparations which may last thereafter up to 24 hours.

Reaction of subjects to nicotine is identical whether water or alcohol is used as the diuretic agent. Smokers showed diminution and non-smokers enhancement of the diuretic response.

Renal tubular transport for tetraethylammonium (TEA) and p-aminohippurate (PAH) is unaffected when ethyl alcohol is given in concentrations compatible with life. However, when alcohol is added in vitro in concentrations of 1.0 to 2.0 M, it produces an increase in TEA uptake of from 50 to 100%. This does not occur when TEA transport is inhibited by anoxia or high concentrations of TETD. As no effect is produced on PAH transport by these concentrations, the ethyl alcohol stimulation appears to be relatively specific for basic substances.

Correction of impaired water excretion has been demonstrated following alcohol ingestion by patients with cirrhosis of the liver. The urine becomes hypotonic and is maximally so at the height of the alcohol level. The disappearance rate of the circulating antidiuretic hormone is not prolonged. Alcohol administered to different patients with a variety of impaired water tolerances, in amounts of between 35 to 60 gms when given singly or between 25 and 40 gms when repeated doses are administered, has a varied effect on diuresis which is independent of the underlying nature of the disease.

Alcohol given to patients with urethritis has no apparent immediate adverse effect but there is an overall adverse effect with exacerbation of symptoms following the withdrawal of alcohol. This occurs during a "hangover" period in which organisms might find decreased host resistance and therefore after suitable incubation of organisms, symptoms may occur.

Chronic alcoholism does not play a part in the etiology of nephropathy. In the absence of other evidence of kidney disease, however, a number of chronic alcoholics, especially after acute intoxication, fail to show normal capacity to concentrate their urine.

Reproduction

No difference in growth rate is noticed in mice given 5% ethyl alcohol in lieu of water. The reproductive performance of females raised on the alcohol solution shows no significant difference in the number of young born alive, in the birth rate or in the weaning rate. However, there appears to be a difference in the percentage of successful gestations of second generation females. When given a free choice of water and alcohol solution, alcohol-raised mice consume less water and more absolute alcohol as a proportion of their total fluid intake. Also, offspring of alcohol-raised parents consume more absolute alcohol than those of stock parents. Using latency and degree of bulbar enlargement and frequency of ejaculation in male dogs as an index of sexual reflex activity, alcohol has been demonstrated to have an inhibiting effect on sexual phenomena. Sperm count and volume of semen does not appear to be significantly altered.

Surprisingly little of scientific merit has been written in this area. The sex patterns of chronic alcoholics is presented under the section on alcohol addiction. The relationship of acute intoxication to sex crimes appears under a discussion of alcohol and crime.

Liver

Alcohol is not a hepatotoxic substance per se as demonstrated by experiments in which there has been a careful control of dietary factors, especially those relating to fat mobilization and deposition. Chronic alcoholism is, however, associated with a higher rate of cirrhoses than any other disease or environmental factor in this country. Also alcohol apparently renders the human liver more susceptible to injury by hepato-toxic agents on exposure subsequent to intoxication. Liver injury due to hypoxia secondary to poor circulatory status, and severe respiratory depression as a result of profound alcoholic intoxication may occur as it does in the kidney. Chronic liver injury secondary to nutritional deficit can be produced experimentally with ease.

In paired feeding experiments rats placed on a cirrhosis-producing diet and fed 20% alcohol solution will have a higher rate of cirrhosis than did those given water. However, chronic alcoholization carried out in rats in which diet and alcohol consumption is carefully controlled does not increase the tendency to develop nutritional fatty livers when the animals are maintained at a low intake of lipotrophic substances. Neither does this procedure accelerate the development of liver cirrhosis which normally follows a sustained fatty liver. A moderate degree of chronic alcoholization does not exert any definite effect on the level of glycogen in the liver, but acute alcohol intoxication causes a definite reduction of liver glycogen except when glucose is simultaneously administered.

Alcohol administered to rats in amounts of 6.2 gm/kg of body weight uniformly results in an increase of liver lipids to an average peak of 7.4% about 15 hours after administration in males, and to a level of 9.4% 18 hours afterwards in females. This increase does not occur when animals are adrenalectomized, but adrenalectomized animals pretreated with cortisone for seven days also show the increase. Removal of the adrenal medulla does not prevent lipid deposition. Experiments with hypophysectomized rats show that the pituitary must also be intact for the accumulation of lipids. It would appear, therefore, that the liver lipid concentration is promoted by an increased output of the cortical or pituitary hormones or both. It is possible that alcohol may cause the mobilization of fat from depots and that these hormones are involved in the mechanism of mobilization.

Other investigators have also found that the concentration of plasma-free fatty acids in rats acutely intoxicated with ethanol is significantly higher over a period of 4 to 20 hours than in controls fed either water or isochloric quantities of glucose. This offers an explanation for the mobilization of fat from depots in consequent fatty infiltration of the liver in

ethanol intoxication. As noted above, this is probably secondary to the release of the adrenocortical hormone, pituitary hormone or adrenergic catechol amines.

Administration of large doses of ethyl alcohol to rats also causes an increase 16 hours later in the liver triglyceride level, of two to threefold that of the normal period. Aspartate or glutamine given simultaneously does not prevent the elevation. However, l-asparagine completely prevents it and alpha ketoglutarate partially prevents it.

Effects on other aspects of liver metabolism indicate that maintenance of experimental animals on 10% alcohol solution reduces the protein stores in the liver by 10 to 15% and the vitamin A stores by as much as 25%. Moderate quantities of alcohol given dogs either by stomach or intravenously produced an increase of vitamin A in the serum which is correlated with the original concentration in the liver. Since injection of alcohol into the portal vein causes an increase of vitamin A in the serum of blood from the hepatic vein, mobilization is apparently accomplished by direct action on the liver stores.

When administered as a 20% solution and the only source of fluid intake, alcohol has been demonstrated to affect the glutamic oxalacetic transaminase activity in rat livers, the significant change being an increase in the GOT:GBT ratio.

Administration of alcohol had no discernible effect on utilization of glucose or levulose. However, lactose tolerance is significantly affected in healthy subjects receiving .4 cc of alcohol/kg 15 minutes before the injection of the sugar. This suggests a highly specific action of alcohol on the hepatic enzyme system involved in handling lactose.

Utilizing the perfused isolated liver and tagged ethyl alcohol, it may be demonstrated that ethyl alcohol will support the synthesis of acetic acid, acetoacetic acid, pyruvic, beta-hydroxybutyric, and lactic acid. Livers from fed animals produce more acetate than fasted animals after ethyl alcohol. In isolated livers of cats infused with ethyl alcohol, glycogen is decreased and lactic acid of the perfusing blood is increased. Both alcohol and blood sugar are burned at fairly constant rates.

Liver catalase does not affect ethyl alcohol oxidation in the rat either in vivo or in vitro. However, methyl alcohol oxidation by rat liver slices is inhibited more than 50%. Xanthene doubles the rate of methyl alcohol oxidation in vitro but does not affect that of ethyl alcohol. In equimolar amounts ethyl alcohol inhibits methyl alcohol metabolism both in rat liver slices and in pure beef catalase system by about 0.5. Methyl alcohol does

not inhibit ethyl alcohol oxidation in liver slices but in pure beef catalase some inhibition is seen on a competitive base. If more methyl alcohol is added, ethyl alcohol can then be inhibited. It would appear that ethyl alcohol itself is not being metabolized by catalase but prevents methyl alcohol from attaching to the enzyme surface.

When 3-amino-k, 2, 4-triazole (AT) is injected intraperitoneally into animals, it causes a reduction in catalase activity of the liver to 8.6% of control. If ethyl alcohol is given prior to AT there is a protective action in that the inhibition of catalase activity is slight. Ethyl alcohol alone does not affect catalase activity.

In examination of the environmental, nutritional and occupational history of clinic patients with cirrhosis, increased ethyl alcohol consumption was found to be associated with 42.5% of cases of portal cirrhosis of the liver with ascites, while in 38.5% of the cases there was no definite etiological factor determined.

Since choline is probably required in some step of alcohol metabolism, liver disease in alcoholics can result not only from choline-poor diets but also because of the extra requirement for this substance.

Presumably healthy, gainfully employed men whose daily consumption of alcohol, according to their own reports, ranged from an occasional drink to one pint a day, were classified into four groups based on the different consumptions. A battery of 11 liver function tests were then carried out. The only finding which showed unequivocal relationship to alcohol consumption was the urine coproporphyrin test. The greater the consumption, the more coproporphyrin was excreted. The findings strongly confirm the opinion that there is no prominent relationship between alcohol consumption and hepatic function in men whose nutrition and health are normal.

In a second study, various liver functions performed in healthy men four hours after receiving ethyl alcohol indicated results to be generally normal. However, in an occasional subject, there occurred a marked increase in the citric acid content of the serum, an increase in the serum bilirubin and moderate coproporphyrin excretion. These investigators postulate that there may be an occasional individual with a sensitive liver and he may be the one who succumbs to the characteristic liver damage seen in chronic alcoholics. The conclusions, though highly speculative, suggest the desirability of further investigation.

The blood alcohol curve of patients with liver disease, including hepatitis and cirrhosis, is reportedly different from the normal alcohol curve in that the maximum level remains elevated for a longer period of time.

In contrast, in patients with obstructive jaundice, the curve rapidly reaches a higher maximum and drops more steeply to normal values.

Skeletal Muscle

Alcohol has no significant effect on striated muscle in vivo or in vitro except in unrealistic concentrations in the latter instance. Sixty to 80% alcohol solutions potentiate the maximum stimulating effect of acetylcholine on striated muscle strips in vitro. The effect which is shared by either is thought to be due to an antiesterase effect.

Like cocaine, amphetamine and other drugs which decrease the appreciation of fatigue under both experimental and actual situations, alcohol causes people to be temporarily capable of greater work output. In contrast during the post-drinking phase, especially in hangover, volunteer test subjects drawn from firemen and policemen were capable of a shorter performance of heavy work as measured by means of a bicycle ergometer. This laboratory data is confirmed by practical experience.

Endocrine Glands

The adrenals have been extensively investigated with reagrds to their activity in the presence of ethyl alcohol. Relatively little is written concerning the other endocrines.

When administered intraperitoneally, alcohol is capable of reducing the cholesterol and ascorbic acid levels in adrenal glands in both rats and guinea pigs, whether administered as a concentrated or a dilute solution. Neither prior nor concurrent injection of sodium ascorbate into these animals fed an adequate vitamin C intake, influenced the initial adrenal response to alcohol intoxication. However, subsequent administration of ascorbic acid did serve to return the adrenal gland ascorbic acid level to control values within four days and to accelerate the restoration of the adrenal cholesterol.

The effect is apparently mediated through the pituitary since hypophysectomized animals do not show the effect. It is concluded that alcohol intoxication imposes a condition of stress on the organism which results in depletion of adrenal constituents.

While normal rats administered single intoxicating doses of ethyl alcohol show a reduction in the level of cholesterol and ascorbic acid in their adrenal glands, animals deficient in pantothenic acid, riboflavin or

pyridoxine do not demonstrate the same adrenal response in relation to this challenge. Rats fed a diet deficient in both tryptophan and niacinamide or lysine also fail to show a definite reduction in cholesterol. Protein deficiency by itself does not alter the normal response.

While single doses of alcohol cause a drop in the ascorbic acid content of the guinea pig adrenal, the effect is less pronounced following a second and third injection, and after repeated injections extending over a period of weeks, providing the animals are allowed access to leafy vegetables, there is essentially no effect and no development of scurvy.

Adrenocortical response in mice as evidence by thymic involution is related in a linear dose response to the quantity of alcohol ingested. The involution of the thymolymphatic system was obviated by adrenalectomy.

Adrenalectomy produces no essential differences in the effects of oral doses of alcohol at the level as regards plasma, potassium, sodium, glucose, hematocrit, sedimentation rate or urine output. There is, however, a decrease in the magnitude of the hypoglycemia which usually occurs.

A few untoward effects of alcohol have been described. Hypoadrenocorticism developed as a response to stress may be precipitated or aggravated by excessive use of alcohol and other drugs. This condition secondarily causes hypoglycemia, which is poorly tolerated by alcoholics and is accompanied by a craving for alcohol.

Golfarb (193) relates the following endocrine pathology in rabbits as due to the excessive administration of alcohol: degeneration of the pituitary; testicular atrophy in males and alteration of gestation period in pregnant females; ovariectomized rabbits had a reduced resistance to alcohol which is restored by estrogens.

Adrenal imbalance has not been reported in acute alcoholism in man. Utilizing the eosinophil drop normally seen following the injection of ACTH as a measurement of abnormal pituitary and adrenal function, Mann (194) was unable to demonstrate any hypo response in a group of alcoholics. He concluded that a defect in the pituitary-adrenal axis is not generally characteristic of alcoholic patients.

Gastrointestinal Tract

The ultimate effect of alcohol on the intestinal tract depends in addition to the concentration and quantity ingested, on a number of other factors. These relate to the quantity and type of food present, the presence of

disease, and other drugs. In small quantities and at low concentrations there is a motor effect on secretion and contractility. Concentrations over 40 percent cause irritation. Prolonged contact causes irritation with microscopically identifiable changes. There is also an effect on emptying time.

Alcohol held in the mouth increases salivation. In low concentrations it increases the secretion of gastric juices, but in concentrations above 5% it retards digestion. The production of pancreatic juice is inhibited by concentrations above 2%.

The emptying time for the passage of glucose from the stomach of rats is delayed in animals intoxicated by acute intravenous doses. This delay is also seen up to periods of three hours when alcohol is given per os and it may be of significant magnitude to play a role in pathogenesis of gastric disturbances associated with acute alcoholic intoxication.

Intravenous alcohol markedly delays the passage of glucose from the stomach since 40 to 80% remain after two hours while none remains in control animals. Intravenously administered alcohol also delays the passage from the stomach of orally administered alcohol.

In view of the reported increased incidence of peptic ulcer in alcoholics, a study was conducted comparing the serum pepsinogen values of hospitalized alcoholics with those of normal controls. This revealed a significantly greater level in alcoholics with a mean value of 248 ug per ml in the alcoholics compared to 187 in the controls. During hospitalization there was a statistically significant downward linear trend in the alcoholics according to the length of hospitalization.

The isodynamic substitution of alcohol for energy giving foods is without benefit for the production of muscular work. Alcohol is without value as a thermogenic agent because its contribution as such is occasional and cannot be regulated. Alcohol is considered as a food insofar as it helps to conserve some quantities of sugar and fats which would be used by the tissues if alcohol were not present. The latter function is achieved only when alcohol is ingested, diluted in small quantities and taken in divided doses over a day. The quantity thus used reaches approximately 1 gm of absolute alcohol per kg for 24 hours.

Immunologic Response

Failure to produce an allergic response to a serum from rabbits administered alcohol or from human subjects with known increased intake have

led Robinson (195) to conclude that ethyl alcohol stimulates neither the development of detectable amounts of anti-alcoholic antibodies nor a detectable allergic reaction. Positive results of other investigators may be due to the production of allergies not to alcohol itself but to other substances present in the beverage.

Ingestion of grain alcohol or whiskey has been observed to increase the size, intensity and duration of allergic wheals in both allergic abstainers and allergic drinkers. The effect is not related to absolute blood alcohol level. Ingestion of alcohol also increases already present passive transfer reactions produced by injection of allergens into sensitized skin sites. In the so-called alcohol-sensitive person the ingestion of alcohol brings to a clinical level a sub-clinical allergic reaction.

Idiosyncrasy to alcoholic beverages as evidence by a weakness, sweating, tachycardia and chills occasionally follow the drinking of even small quantities. The reason has not been elucidated.

Occasionally there are reported other unusual reactions following ingestion of a small amount of alcohol. These include flushing of the face and neck, congestion of the conjunctiva and cornea. Additional amounts of alcohol have not increased the reaction, which lasts about one hour. Postulated mechanisms include stimulation of histamine release by alcohol ingestion, and an existing allergy precipitated by the vasodilating effects of alcohol.

No biochemical relationship between idiosyncrasy to alcohol and allergic reactions due to sensitization to foreign proteins has been found in problem drinkers.

VI

THE ENVIRONMENT

Decreased Pressure

A limited amount of data relative to the lowering of barometric pressure appears in the medical literature, though nothing relative to increased pressure has been found.

McFarland (196) demonstrated that the effects of alcohol are greatly accentuated at high altitudes. Inefficiency following the ingestion of alcohol is therefore impaired proportionately. He reported that alcohol is oxidized more slowly and subjective effects are accentuated when air deficient in oxygen is breathed.

Newman (146) examined the effects of altitude on alcohol tolerance utilizing a gas mixture of 10% oxygen and 90% nitrogen which he assumed as equivalent to an altitude of 18,000 feet. Reduction of motor coordination as measured by a pursuit meter was utilized as a test of the alcohol effect. None of the subjects showed any deterioration of performance in the absence of alcohol, though breathing only 10% oxygen. In three of five subjects there was a striking reduction of the alcohol concentration in the blood at which a significant deterioration of performance occurred when the low-oxygen mixture was breathed. Two subjects showed no significant change in their thresholds.

Utilizing flicker fusion frequency as a criterion of impairment, the majority of subjects tested in a decompression chamber at a simulated altitude of 10,000 feet showed impairment at levels of .03% alcohol, a concentration which did not affect the fusion frequency at normal pressures. The effect of alcohol was greatest at one hour, while that of hypoxia alone was greatest between two and four hours. The combined effect of alcohol and hypoxia was greater than that of either alone.

Hypoxia induced by breathing oxygen-deficient air simulating altitudes between 3900 and 5900 meters above sea level reduces dark adaptation in some subjects. Alcohol does not significantly influence changes brought about by hypoxia according to these studies, and the undulations of the curve seen in subjects after the ingestion of alcohol persist in those subjects in whom the thresholds are increased by anoxia.

In other tests on vision, alcohol was found to produce more consistent results than hypoxia; the two together cause a potentiation of effects. The principal changes were a tendency to endophoria (far vision) and conversion insufficiency in near vision.

Using as an end point the time lapse from the beginning of decompression until apnea occurred, intoxicating doses of alcohol in rats does not summate with severe anoxic anoxia produced through decompression to hasten terminal functional breakdown in the neurons governing respiration. There was, however, no evidence whatever that alcohol enhances tolerance to hypoxia as has been suggested by Emerson (197). Deleterious effects of alcohol and deompression hypoxia might be demonstrated if end points other than apnea or death could be chosen. The problem of alcohol-hypoxia summation is in need of clarification.

In one study mice exposed to hypoxia in decompression chambers at altitudes up to 40,000 feet showed increased survival rates when pretreated with ethyl alcohol one hour prior to exposure.

High altitude polyuria develops in animals fed 5-10% alcohol solutions as the only drinking fluid, and is relatively as great as the water polyuria in controls. Alcohol given in this manner is not diuretic in animals exposed at altitudes equivalent to only 15,000 feet.

Saviano (198) reports that no differences are noted in the utilization of alcohol in normal or diabetic dogs when glucose is injected with alcohol at either sea level or under decompression to 450 mm of mercury barometric pressure. However, in the absence of glucose, diabetic dogs which received alcohol show greater impairment at decreased barometric pressures than at sea level.

Leonardi (199) reports that 30% of a test group of young, healthy men subjected to hypoxia and administered alcohol have slower oxidation rates of alcohol than normal, and this he equates to a decrease in carbohydrate metabolism secondary to anoxia.

Data regarding the effect of reduced pressures on endogenous alcohol are contradictory. Saviano (200) determined endogenous alcohol and blood sugar levels in 20 healthy men under normal barometric conditions and in a decompression chamber after one hour at 450 mm. In 14 of the subjects sugar and alcohol values rose, the latter reaching as high as .08%.

The endogenous alcohol levels in animals placed in a decompression chamber at a total pressure of 500 mm of mercury, markedly increased over baseline values ranging between .02 and .11%. Blood sugar values simultaneously rose in the majority of animals, and it has been concluded that there is a close relationship between mobilization of glucose reserves and increase in endogenous alcohol concentration under conditions of oxygen deficiency. However, utilizing GLC techniques and exposures of six human subjects to simulated altitudes of 4,000 M for two hours and four rats to 7,000 M for five hours, other investigators reported it was not possible to increase the alcohol concentration or that of any other carbonaceous material appearing in the expired air.

A possible explanation of the lower concentration of alcohol in whole blood and plasma following standard doses of alcohol in persons at atmospheric pressures reduced to 470 mm revolves about increased pulmonary elimination of alcohol following hyperventilation. No difference in whole blood concentration was found, and it is not related to the increase in the number of red cells caused by barometric decompression.

The majority of effects of environmental temperature are mediated through changes in body temperature itself. There also appears to be a critical environmental temperature above which a given drug may produce

a rise in body temperature and below which it produces a fall. It is suggested that the increased toxicity of both high and low environmental temperatures result from interference with temperature regulation and that among substances having a greater toxicity at lower temperatures is carbon monoxide. Body temperature changes may also affect the duration and intensity of action of a drug. There has been apparently very little investigation of the action of depressants on the CNS at low temperatures. Some of the effects, however, at low body temperatures may relate to changes in the rate of detoxication. Thus the body temperature becomes important as a determinant in the duration and intensity of action of the substance. The rate of oxidation of ethyl alcohol is reported to increase during hyperthermia, while hypothermia tends to decrease the rate of absorption but also increases the rate of oxidation of alcohol.

Cold

In review of causes of accidental deaths, Jellinek (201) has indicated that alcoholism is both a primary and secondary cause. In those deaths due to excessive cold, excessive heat or acute accidental poisoning, alcoholism is an associated cause at an extremely high incidence, much higher than the presence of alcoholism as a contributory to other accidental deaths. It is a long-held medical belief that chronic alcoholics furnish an excessively large proportion of deaths in excessive cold, due in part to the disregard of the danger and in part to a lowered resistance to cold.

Ethyl alcohol given in high doses to mice prolongs survival time when these animals are submerged in water at 25° and 45° C respectively. The findings are in agreement with previous experiments on prolongation of survival in anoxic deaths due to explosive decompression.

Rabbits receiving alcohol solutions orally and then subjected to cold for a period of seven hours either immediately or after one hour, had decreased absorption of alcohol into the blood stream and a slowing of the elimination time while in the cold. The latter finding is at variance with results obtained by others in rats.

There is an increased rate of alcohol utilization by rats kept at 2° to 5° C, but a smaller increase in oxidation when tryptophan-niacin deficient animals are placed in a cold environment.

Dybing (202) demonstrated a distinct difference in the utilization rate of alcohol in rats whose rectal temperature was reduced to 20° C in comparison with normal animals maintained at 40° C. The rate of disappearance of alcohol from the blood is three times as great in normal animals.

Oxygen consumption of cerebral cortex slices from albino rats measured in vitro was increased at the unphysiological concentrations of 2% alcohol at temperature levels of 37.7°, 30° and 20° C. At higher concentrations the percentage in additional oxygen uptake with a given concentration of alcohol decreased with decrease in temperature, and was absent at 20° C. There is a large range of alcohol concentration from 8 to 25% in which the rate of oxygen consumption was approximately constant.

Environmental temperature of between 2° and 5° C has no effect on the drop in adrenal cholesterol following alcohol administration. However, animals fed tryptophan-niacin deficient diet for three weeks and challenged with an intoxicating dose of ethyl alcohol fail to show this drop in cholesterol. When additional challenge in the form of still lower environmental temperatures is given, the drop also occurs. Cold stress has no significant effect on mortality in the diet-deficient animals. However, when alcohol intoxication is superimposed on cold stress, these deficient rats became more susceptible with a mortality of 35%.

Utilizing time as an indication of proficiency in a specific task, the dissembling and reassembling of Brush-Assembly Breakdown, basic airmen have no differences in the time required to complete the work at temperatures as low as -40° F. However, the total lapsed time is decreased following ingestion of the equivalent of two ounces of distilled spirits. This time difference occurs since the majority of test subjects do not take time to warm their hands. Whether this effect is due to peripheral dilatation or to the analgesic properties of alcohol has not been ascertained.

Schulze (203) reported that the vasodilatation could be produced in the middle finger of otherwise gloved-hand subjects exposed to temperatures as low as -18° C in about 40% of subjects receiving 100 cc of rum and 90% of subjects receiving 200 cc of the beverage offered as a hot drink. Vasodilatation in the feet occurred more sluggishly and the effect of alcohol on the peripheral vasomotor system was dependent on the activity of the thermo-regulatory center. Under conditions leading to a negative heat balance, alcohol has little influence on local cold effects because of highly increased vasomotor tonus. In evaluating the prophylactic use of alcohol in exposure to cold, the psychological effects of alcohol must be taken into consideration; since many people react with fatigue, efficiency may be lowered and attempts at protection abandoned. Muscle tremor also decreases with increased alcohol intake and thus lowers production of heat. The usual objection, however, that vasodilatation due to alcohol increases heat loss is not considered as important. The prophylactic use of alcohol against freezing is therefore debatable but its therapeutic usefulness in cases of local freezing is accepted.

Artificially induced hibernation was attempted in the treatment of acute delirium by administration of ganglioplegic drugs and refrigeration of the patient at 34° C for three days. Two of three patients treated in this way died; when the duration of refrigeration was reduced in five additional patients, all recovered.

Increased Temperatures

The effects of temperature on the action of drugs has been reviewed by Fuhrman (1, 2) with the generalization that there are three common relationships. In the first, minimum toxicity occurs at some temperatures usually around room temperature and toxicity increases at temperatures below and above this point. In a second instance a continuously increasing toxicity occurs with increasing temperature. In a few instances there appears to be essentially no effect over a wide temperature range and then a sudden increase as temperatures exceed the critical point.

Nicloux early demonstrated that the metabolism of alcohol in the frog increases with rising temperatures. However, attempts to increase the metabolism of alcohol by means of thyroxin, dinitrophenol or exposure to cold did not significantly alter the rate of oxidation in homeotherms. Fuhrman demonstrated that the rate of combustion of alcohol in rabbits at 25° C was 100 mg/kg per hour as compared to a rate of 156 mg/kg per hour in animals with temperatures of 38° C. He concludes that the rate of alcohol metabolism is dependent upon body temperatures both in homeotherms as poikilotherms.

In experiments employing both the increase of body heat by external and internal means, it has been reported that dinitrocresol increases the rate of disappearance of alcohol. The absorption of alcohol is accelerated by both treatments and dinitrocresol increases the elimination of alcohol through the lungs, while external heat influences it only slightly. The concentration of alcohol in the blood decreases slightly more rapidly following hyperventilation. In guinea pigs there is an increase in 19% of the quantity of the alcohol eliminated through the lungs after the animals had been administered dinitrophenol. However this amounted to elimination of only 3.5% of the total alcohol dose, and is not a significant factor in the overall disease.

The induction of therapeutic fever and excessive perspiration has been reported to increase the disappearance rate of alcohol from 43 to 125% in man. Some of this increase is due to the increased elimination of alcohol through the kidney and sweat glands but the principal reason is believed to be the increase in metabolism produced by the therapeutic fever.

VII

MEDICOLEGAL PROBLEMS

Introduction

Public intoxication is responsible for 40% of all arrests in the U.S. This amounts to over 840,000 such charges among 2,000,000 arrests for various crimes in 1956 in cities over 2,500. In New York, however, public intoxication constitutes only 3% of arrests. The drunken man is charged with disorderly conduct and the Department of Welfare furnishes free facilities for day-to-day subsistence for these men. This lessens the necessity for a penal approach and public opinion tends to be less hostile. Alcoholism thus becomes a public health problem rather than a police or judiciary problem.

Divergent views are held concerning association between alcohol and crime. Lukas (204) attempting to resolve this has proposed the following view: "Crime is a symptomatic underlying behavior disorder produced by the mixture of many factors. Alcohol constituting a means of escape from painful reality brings out an intoxication state by which the influence of inhibitions are excluded." Emotional instability and conflict within the environment are among the principal characteristics of the criminal offender. Alcohol as a mechanism for dissolving controls is, like crime itself, a manifestation only of an underlying disorder.

In the investigation of over 1,000 cases of medicolegal importance, Hansen (205) reports that blood alcohol levels above .05% were present in 32% of traffic cases, 9% of industrial accident cases, 41% of general accidents among adults, 32% of suicides, and 20% of adult cases of sudden unnatural death. It is recommended that alcohol determinations be made routinely in all cases of sudden death.

Reports from the United States as well as various other countries show a wide fluctuation in the involvement of alcoholic consumption in those committing criminal acts in general, and specific types of criminal acts in particular.

According to statistics from the Department of Legal Medicine from Harvard Medical School, about 50% of persons homicidally slain had been drinking. Wolfgang (206) has reviewed the events surrounding over 500 homicides in a metropolitan area in the eastern United States as they relate to the presence or absence of alcohol in offenders and victims. A study of detailed breakdown according to time, race and general use of alcohol in

the community is included. Unfortunately the tissue level of alcohol in the victims or participants in a crime was not recorded and the degree of alcohol intoxication could only be defined in terms of descriptive events prior to the crime, and the reports from witnesses, defendants and police. The conclusions of the author are that in a high percentage of homicides, alcohol is a factor in the behavior of the victim and perpetrator of the crime.

Following a study of patients in the prison ward of a psychiatric hospital in New York, Winkler (207) concluded that primary alcoholism was responsible for felonies in only rare cases, but that alcohol intoxication often precipitated crimes. He concluded that offenders on probation and persons with organic brain disease should remain totally abstemious.

In a review of records of 10,000 persons under the age of 17 who were contacted by police on various complaints, only 141 boys and 73 girls had arrest records involving drinking. The study reveals that adolescents known to be involved in episodes of drunkenness are much the same kind of youngsters as those who engege in other juvenile offenses. In general those involved with alcohol are of the older age of juvenile delinquents. A follow-up of police records demonstrates that at least 10% of these juveniles arrested for drinking had later engaged in a pattern of anti-social behavior in which heavy drinking was an element.

Of 882 persons arrested during or immediately after the commission of a felony during the years 1951 to 1953, 64% had at least .1% of alcohol in the urine. Among those charged with crimes of violence, the figure reached 88%; 45% of those were charged with rape and 43% were arrested for felonious assault.

Data compiled from various countries in which percentage of accidents involving alcohol have been recorded, shows that in industrial accidents, approximately 6% of the persons have blood alcohol levels between .03 and .11, and 4% between .11 and .22%.

Alcohol was present in 16.7% of all cases tested in a coroner's jurisdiction in California where all referrals were subjected to medicolegal examination. Alcohol was found responsible for death in 3 cases and contributory in 116.

In analysis of murders committed in Ceylon in 1940, less than 10% of the offenders were under the influence of liquor.

Alcoholic intoxication was reported to play a role in 60 to 80% of all crimes in Bulgaria. In 19 of 48 cases, murder was committed during pathological intoxication which was proved by test.

Among 6,612 men and 503 women tried on criminal charges in Sweden in 1947, 39% of the men and 4.2% of the women had committed their offenses while "under the influence of alcohol," and 37% of the men and 3% of the women were known misusers of alcohol. Misuse of alcohol was more common among older offenders and among males and those who were habitual rather than first-time offenders. The highest percentage of misuse was among those who commit petty offenses and was rarely found among those who committed planned crimes such as forgery or embezzlement. There was an increase in crime as well as the misuse of alcohol since the abolition of the rationing system in Sweden in 1955.

In 74 (15%) of 500 attempted but unsuccessful suicides, alcoholic intoxication played a role; the cases could be divided into three groups. In the first, the person happened to be intoxicated at the time of the attempt and it was not premeditated. Second, the person reportedly drank alcohol to enable himself to acquire courage for the premeditative suicide, and the third group was composed of alcoholics. It is apparent that alcohol plays an important part in suicidal attempts.

Analysis of 100 consecutive cases of male sex offenders indicated that 8% of the total were chronic alcoholics, 35% had been drinking at the time the offense was committed, and in the remainder there was no over-alcoholic indulgence.

Rotman (208) has reported that alcoholism in sex crimes converges dramatically in the psychopathic personality. A major portion of the pseudostimulation by alcohol in such individuals is a false stimulation of the libido. Hence the close relationship between acute intoxication and sexual psychopathies. In chronic alcoholism there are frequently delusions of infidelity. Of 29,000 cases referred to the laboratory of the Psychiatric Institute of the Municipal Court of Chicago in a 10 year period following 1936, 23.7% fell into the category of alcoholism.

Psychbiological reactions to alcohol in some individuals may lead to acts of a criminal nature. Punishment which follows will satisfy the individual's feeling of guilt, but society will not accept punishment as cancellation of the crime. If drinking was in any associated with a criminal act, the prisoner should never drink again whether or not he feels he has an alcohol problem.

Mitigating Effects

Drunkenness is not accepted as insanity in most legal jurisdictions; however, chronic insanity resulting from inebriation will exonerate an individual from full responsibility for his acts.

Whether alcoholism is a disease in itself or a symptom of another underlying disease is unimportant in the legal sense. The judicial mind is presently convinced that chronic alcoholism is a self-inflicted injury and not a disease within the meaning of disability provision. There is need therefore for a statutory presumption against chronic alcoholism as an intentional act or non-disease.

Drunkenness is no excuse for a crime of negligence, but intoxication has been admitted in evidence to show lack of intent or even knowledge of facts in criminal action. Voluntary drunkenness is acceptable in an addict suffering from brain damage caused by alcohol from delirium tremens and on occasion when alcoholism may be considered as a symptom of mental illness.

Michel (209) distinguishes three types of intoxication for legal purposes: simple drunkenness, characterized by moderate excitement and negligible amnesia; complicated intoxication manifest by violent excitement and marked decrease in mental functions, though maintaining contact with reality; and pathological intoxication, manifest by confusion, lack of relation with the environment, extreme anxiety and nearly complete amnesia. The second form may be regarded as somewhat attenuating circumstance in crime, while the third condition is legal insanity.

Pathological intoxication characterized by abnormal behavior following relatively small amounts of alcohol and amnesia for the episode, is considered a form of psychosis and the individual is therefore not held responsible for his actions. It is difficult for courts to understand the difference between pathological intoxication and ordinary drunkenness. The condition has been considered as an expression of uninhibited psychopathy which is exemplified by similar EEG patterns to psychomotor epilepsy. The subconscious motivation absolves the person of criminal responsibility. Structurally the cortex of the brain is held as legally responsible, while the basal ganglia and midbrain are not. Though this situation is extremely rare, pathological intoxication does occur and the criminal responsibility of the pathologically intoxicated person must be viewed in a different light than one who has willingly become intoxicated. There are states of disordered consciousness due to alcohol, even though the law does not accord the same recognition of freedom from responsibility when alcohol is involved as it does in other cases. It is generally accepted that a person, whether he is an habitual drinker or not, cannot voluntarily make himself so drunk as to become on that account irresponsible for his conduct during drunkenness. He may be perfectly unconscious of what he does and yet he is responsible. He may be incapable of expressing malice but the law implies malice and in such a case the nature of the instrument used, the absence of provocation, and other circumstances under which the act is

done must be considered. The incapacity of the defendent to deliberate and premeditate at the time the act is committed may be taken into consideration and thus reduce a degree of guilt from murder in the first degree to a lesser crime.

Marinacci (210) has suggested, therefore, that in forensic cases when there is suspicion that a crime may have been committed during a state of altered consciousness produced by alcohol, and there is reason to believe there is some pathological response to this substance, EEG's should be taken under a test situation after the ingestion of alcohol.

According to Navy court-martial orders, the terms "drunkenness, intoxication under the influence" are synonymous. The degrees of intoxication are not distinguished.

A patient who is persuaded to submit to treatment by a physician known to be grossly intoxicated and who suffers injuries because of improper treatment due to the physician's condition is guilty of contributory negligence as a matter of law and barred from recovering damages for malpractice, according to the North Carolina state rulings. The contributory negligence applies only in civil cases; in the event of a criminal charge, the doctor would be held responsible. Therefore a person is not excused from crimes committed under the influence of alcohol, but intoxication may serve to lessen the punishment.

Diagnosis of Intoxication

There are two large series which critically compare the findings of the blood alcohol level with the results of clinical signs and symptoms regarding alcohol intoxication. Expressed as the percent of persons intoxicated, Jetter's group (75) has a considerably higher percentage so designated at levels of .2% than does Newman's (150) though at .3% and above, 95 to 100% of both groups were intoxicated. The explanation for the difference in these figures lies in part in the composition of the groups studied. In Jetter's series, subjects included both men and women of different physical status, while in Newman's groups the subjects were for the most part vigorous, healthy males.

From both the medical and legal standpoint it is desirable to consider the matter of subclinical intoxication. This state is accepted as existing when there is present in an individual, due to the presence of ethyl alcohol in his brain, a state of impaired nervous system function sufficient to significantly influence the task he is performing, but not accompanied by such gross changes of behavior, coordination and appearance that the examining

physician need entertain the diagnosis of drunkenness. In this respect the comments of the British Medical Association are pertinent.

The word "drunk" as defined by the Committee of the British Medical Association indicates that "the person concerned was so much under the influence of alcohol that he had lost control of his faculties to such an extent as to render him unable to execute safely the task in which he was engaged at the material time."

The lack of definitions of what constitutes "intoxication", "drunk", or "under the influence" gives rise to medicolegal problems. While alcohol at high concentrations unquestionably may impair judgment, change coordination and reflexes, and alter the basic behavior pattern of people, it is the minimal impairment of functions occurring in early stages of intoxication that leads to conflict with the law, and this at a level at which people are frequently involved in accidents but may show so little signs of gross intoxication and have consumed such a small amount of alcoholic beverage, that the decision as to their degree of intoxication is difficult to achieve.

This concept which equates drunkenness and subliminal intoxication is useful in reviewing the following reports regarding the diagnosis of the driver impaired by alcohol.

Lambercier (211) summarized the findings of 30 investigators with over 30,000 subjects regarding the relationship of concentrations of alcohol in the blood with clinical signs of intoxication. Psychological experiments on the effects of various doses by some 53 investigators have been reviewed and, based on these findings, the author concludes that blood alcohol levels between .08 and .11% definitely are indicative of the diminished ability to drive.

Of a series of persons suspected of driving under the influence of alcohol, 90% had blood alcohol levels lying between .15 and .25%. Evidently operators with such concentrations are most liable to arrest. In 85 to 95% of the patients, agreement between the chemical tests for intoxication and clinical effects of alcohol was good. Occasionally an individual with .3% or more of alcohol showed no clinical signs of intoxication. These persons should be classified as "under the influence" on the basis of the chemical test alone, according to Davis (12).

Heise (128), reporting on the AMA's committee to study problems of motor vehicle accidents, recommended that the percentage of alcohol in the blood be used as a reliable index of the degree of intoxication, especially when considered together with clinical symptoms. Standards quoted in 1938 were: 1) below .05 indicates the temperate driver; 2) the wide

middle-road range of .05 and .15% considers tolerance and idiosyncracy; 3) the highest zone greater than .15% indicates alcoholic influence regardless of unusual tolerance.

As accurate as the chemical tests may be, efficient clinical examination in conjunction with blood alcohol estimation gives results that are more reliable than those given by either tests alone or no tests at all.

Prag (212) examined 100 persons charged with driving under the influence of alcohol and found that none of those with blood concentrations of less than .05 showed clinical signs of intoxication, while 23% of those with between .05 and .10 showed this and 94% of those with blood alcohol concentrations above .15 were intoxicated. He also noted signs of intoxication present at lower blood alcohol levels in abstainers than in heavy drinkers, with moderate drinkers occupying the intermediate position.

Smith (213) in analysis of over 500 drivers involved in personal-injury motor vehicle accidents in Toronto in 1950, indicated a marked correlation between driving error and alcohol concentration. Blood alcohol levels as low as .03 and .05% were found to contribute to errors in driving situations.

Lofthus (214) reported on the results of physical examination of approximately 1,000 individuals over a period of 15 years for the purpose of determining whether they were under the influence of alcohol to the extent they would be unable to drive a motor vehicle. The clinical diagnosis of "not sober" was based on a multitude of symptoms and observations which for the most part are not readily quantifiable. In extreme cases this leads to surprising results, as in the unusual individual who is considered sober in spite of a blood alcohol level of .257% and, on the other hand, a person with a .00% found not to be sober. This study was done in Norway, a country where the level of .05% blood alcohol is considered as indicating that a person is so impaired that he is unable to drive. The question was raised as to whether the level should be lowered to .03%. It was concluded that the number of cases in the critical blood alcohol class below .05% was too small to justify statistical treatment and the material presented could not be said to offer an answer to the question.

Many different types of diseases and injuries may simulate alcohol intoxication. Alkalosis, in which the patient becomes restless, fidgety and reportedly confused, has been mistaken for acute alcoholism. Warning has been issued concerning mistaken diagnosis which can be corrected by application of a breath or blood alcohol test.

Greenberg (7) defines an intoxicating beverage as one that may produce a state of abnormal behavior when accompanied by an alcohol concentratio

in the blood of .15% or more. The amount of a beverage which must be drunk over any given period of time to cause intoxication is expressed by the formula 8 + H = number of ounces of distilled spirits required, where H is the number of hours over which the drink extends. In considering fortified wines this formula becomes 18 + 2H, in the case of ordinary wines 36 + 4H, and in the case of beer 80 + H. Dr. Greenberg assumes that the majority of people cannot reach a blood alcohol level of .15% because of the quantity of beer which must be consumed.

Based on these calculations, other factors being equal, it is possible to make a fair estimate of the likelihood that a person may or may not be intoxicated, if one knows the drinking history.

It may be concluded from the experience quoted above that the diagnosis of intoxication is sometimes difficult and that evidence in addition to clinical appraisal by a physician, the lay judgment of a peace officer, or a history of the drinking pattern, is valuable.

As early as 1914 Widmark (215) recommended confirmatory tests in the diagnosis of intoxication. These tests are carried out by a variety of chemical and physical methods. The majority of chemical methods are based on the distillation of alcohol from the sample being examined, oxidation by means of an excess of standard reagent, quantitative measurement of the amount of oxidizing agent remaining, and calculation of the quantity of alcohol present.

In addition to chemical tests, the biological tests which utilize the alcohol dehydrogenase enzyme system are relatively specific under the conditions for analysis for ethyl alcohol. More recently physical methods have been developed which analyze for the presence of alcohol by means of gas liquid chromatography. This last method has many features recommending it, namely the small quantity of sample which is required for analysis, its extreme accuracy and the differentiation from other volatile materials simultaneously in the same specimen without complicating manipulation. A number of samples of body materials have been used for analysis, the most common being blood, urine, and breath; saliva has been taken on occasion and in postmortem specimens, brain tissue is frequently chosen. The majority of analyses are carried out on blood, since so much of the supporting data regarding behavior and coordination have been correlated with the concentration of alcohol in this body fluid. However, there are accurate methods of indirectly determining the blood level based on analysis of other body fluids.

It is, or course, the brain level itself which is of significance insofar as impairment is concerned. While much criticism has been directed

towards the determination of alcohol in the breath, based on such factors as the variations in body and breath temperature, the blood:breath alcohol partition ratio, and the alveolar carbon dioxide level, by and large the newer methods have overcome previous complaints, and in the hands of capable analysts they furnish an accurate method of analysis. The great advantage of this is that there is no difficulty in obtaining samples, and that analysis can be run almost on the spot, immediately on obtaining the specimen.

The four common methods of breath analysis generally used are classified according to the instrument names: the Drunkometer of Harger, the Intoximeter of Forrester, the Alcometer of Greenberg and the Breatholyzer of Borkenstein. The great advantage of chemical tests as an aid in diagnosis of intoxication is that supporting objective evidence based on the results of this test can be used to interpret the degree of inebriation of the person whose sobriety is questioned. Based on the comparison of alcohol levels in the air and tissues as related to thousands of cases on which clinical observation and experimental assessment of impairment has been obtained, it is possible to predict with accuracy at certain levels the relative degree of impairment of this individual without making an individualized test on the person himself.

Dubowski (216) in a review of factors which are raised concerning the reliability of chemical tests, has indicated that these are generally directed towards the integrity of the specimen insofar as contamination with alcohol or other materials which could be erroneously determined as alcohol are concerned, the medicolegal integrity of the specimen as regards its chain of evidence, its identity in relation to the person from whom it was obtained, and the question of the level at a time finitely different from that when the blood sample was collected.

The National Safety Council's Committee on Tests for Intoxication carried strong recommendations as early as 1938 that chemical tests of body fluids or breath be used in all cases civil or criminal in which the influence of alcohol was suspected, that states adopt a statewide system of testing and legislation dealing with the use of evidence obtained from chemical tests, and that legal definitions of "under the influence" be made uniform. They recommended at that time that all persons with a blood alcohol concentration above .15% should be considered as under the influence and that persons with levels below this and not below .05% should be prosecuted only when circumstances and results of physical examination indicated impairment. Shortly thereafter the American Medical Association directed its Committee on Medicolegal Problems to study the problem, and this group made similar recommendations with regards to establishing uniform standards of blood alcohol levels connoting intoxication.

Berry (217) in 1942 urged that communities which planned to use chemical tests should educate the public relative to the objective criteria and impartiality of this procedure, and that a study of the relationship between alcohol concentration and degree of intoxication should be continued through making tests on persons injured or killed in accidents.

In 1943 Ladd (218) pointed out the difficulty of obtaining convictions in cases of driving offenses involving alcohol, stating that chemical tests of alcohol concentration should be used in supplementary evidence, but not in place of the usual evidence introduced. He discussed medicolegal problems relative to the obtaining of specimens, the avoidance of disinfectants, and maintenance of continual possession of the specimen, and suggested simple procedures to be followed for the optimum presentation of evidence.

Yet in 1946, 24 states till had no legal definition of "intoxicated"and "under the influence." In those states which had legal definitions, there were differences distinguishing between "intoxication", the more serious condition, and "under the influence", meaning a lessening to the slightest degree of the ability to perform a certain act. In states, typified by California, "under the influence" was defined as any abnormal mental or physical condition caused by indulgence in alcohol which impairs to an appreciable degree the ability of a driver to operate his car in the manner of an ordinary prudent and cautious person. The California type of law, according to Newman (145) makes prosecution more difficult but tends to punish that individual who, in achieving a certain concentration of alcohol, by reason of his susceptibility to the substance and his lesser initial skill, has such a lowering of his capacity for the task at hand that he is no longer able to perform it in the manner required in his community.

The increased use of chemical tests of blood, urine or breath for alcohol shows a definite trend towards a higher conviction rate on criminal charges on "driving under the influence". On examination of police reports, it is seen that considerably higher percentage of guilty pleas occurs when chemical test evidence is used. It should be acknowledged that the introduction of chemical tests evidence in charges of driving under the influence of alcohol might be expected to alter the disposition of cases, particularly because of increased ability of the police to screen out those cases in which prosecution is not warranted.

The physician has a dual role as regards the drinking driver. He is frequently called on to assist in determining whether a person suspected of inebriation shows clinical signs of intoxication, or to obtain a blood specimen for subsequent analysis.

There is no legal obligation for the private practitioner to render services when called to examine a driver suspected of being drunk. The physician should ascertain that the driver wishes such an examination and in fact agrees to it. While there is no uniformity of legal opinion as to the liability of a physician to charges of assault if he draws a blood specimen without written consent, it is generally advisable for him to obtain this.

Beyond this, however, as Selling (219) has pointed out, the physician has responsibilities regarding the alcoholic who drives. Since the attitude of mind responsible for an individual's becoming a chronic alcoholic also leads him to behave dangerously in the field of driving, the physician should attempt to educate such a person to understand the situation and give up driving. Failing this, the physician should report the patient to the proper authorities and have the patient's driving license revoked. If called in the capacity of a family physician to testify regarding the medical conditions responsible for impaired driving in an acute alcoholic, the physician should remember there is as much justification for revoking the driving license of a drunken driver as of an epileptic, a person using drugs to excess, or one with heart disease.

Vehicular Accidents

The extent to which alcohol is responsible for road accidents can be assessed in indirect ways by using circumstantial evidence. Where taverns are closed on Sunday the relative occurrence of accidents attributable to intoxication is lower. On analysis of fatal accidents in one portion of England, at least one person involved in the accident had been drinking in 18% of all cases and in 60% of those that occurred after 10:00 in the evening.

It is difficult to say exactly how many motor vehicle accidents are due to alcohol because most accidents have a combination of causes. In 1939 official reports showed that one out of every five drivers or pedestrians involved in fatal vehicular accidents had been drinking. One-third of the drivers or pedestrians injured or killed had sufficient alcohol levels to impair their driving or walking. Drivers with a .15% blood alcohol were some 55 times more likely to be involved in personal-injury accidents than drivers without alcohol.

Comparison of a group of persons convicted of driving a motor vehicle while under the influence of alcohol, with offenders against the criminal code, show marked differences as regards sociological and psychological composition. In general, motor law offenders are characterized as people of intermittently high alcoholic consumption at comparatively short intervals, and the drinking habit has led to an attitude of indifference towards the prohibition of driving while under the influence of alcohol.

One hundred of 248 offenders referred to psychopathic clinics because of bizarre behavior or frequent arrest were found to be alcoholics in terms of repeated consumption of alcoholic beverages or daily consumption in more than usual amounts. If all offenders who passed through the traffic court were referred to such a clinic, the number without psychopathology is estimated to be 95% of the total.

Reports from all over the world indicate that the problem is not peculiar to the American culture. Of all deaths in Denmark involving traffic accidents, 45% concerned bicyclists in early 1940's and recommendations were made that the cyclist as well as the motorist be examined for his blood alcohol level. More than .1% alcohol was found in the blood of 44% of a series of 174 individuals injured in traffic accidents.

The risk of incurring a traffic accident is exponentially related to rise in blood alcohol levels, based on statistics relative to accidents in Paris in auto fatalities. More than half the males injured fatally in traffic accidents in 1951 had significant concentrations of alcohol. From a number of European sources statistics indicate that over 19% of those injured in traffic have blood alcohol levels between .1 and .19%, and in another 27% the concentration is .2% or more.

Bowden (220) commenting on the results of analysis for alcohol in a series of medicolegal cases in Melbourne, Australia, between 1951 and 1956, indicated that a third of drivers suspected of being under the influence of alcohol had levels over .25% in their blood and only 6.5% had less than .15%. In fatal accidents approximately 50% of drivers and pedestrians had more than .15%. A similar relationship was demonstrated in coroner's cases among victims dying of burning, drowning and falls.

According to police records, accidents involving drinking constituted 0.63% of all road accidents in England, 0.85% in Wales and 1.9% in Scotland during the year 1953. The proportion of drivers over 60 involved in drinking accidents was greater than the proportion of younger drivers.

Alcohol accounted for between 5 and 6% of all vehicular and pedestrian accidents in Rhode Island in 1939 and 1940. Death resulted in 2.7% of the total accidents and 18.2% of accidents occurring among drinking drivers. Approximately four times as many fatalities occurred among drunken drivers as drunken pedestrians.

Approximately 50% of the 500 persons killed consecutively in highway accidents in Baltimore between 1956 and 1959 had .05% or more of alcohol in the blood. Among drivers having alcohol, the greatest proportion were in excess of .15% and this was also true among pedestrians.

Mozes (221) reporting on 100 drunken drivers in Ohio indicates that such arrests constitute 9.7% of the total arrests from moving vehicle violations, but 46% of serious infractions.

We may conclude that not only the frequency but the severity of accidents increases with rising alcohol levels in the blood. While the correlation is highest in single car accidents, pedestrians and cyclists are obviously affected.

Criticism of Chemical Methods

A number of attacks have been made on the reliability of chemical methods for determining intoxication. These generally are directed toward differences in individual tolerance, the illegality of introductions of the specimen, errors in performance of the test, and failure to identify the sample in evidence with the occurrence.

In his earlier work Newman (145) raised many questions regarding possible errors and their avoidance. He maintained that the concentration of alcohol in body fluids and tissues is not always a reliable index of the degree of intoxication, since the latter may depend on the time at which a certain concentration had been achieved, individual tolerance, nervous stability and initial skill. He suggested that for the highest degree of accuracy in determination of intoxication, three types of evidence should be produced: witness testimony, clinical evidence by a medical examiner, and chemical tests. Since the same degree of intoxication may cause a man to become a potential offender if he drives an automobile and be perfectly innocuous if he remains at home, the type of activity performed must be considered in establishing a diagnosis of intoxication.

Mead (222) suggests that the military chemical tests of concentration of alcohol in the blood fluid are of corroborative value only, because of individual variation in initial and acquired tolerance. Mirsky (223) has concluded further that the central nervous system is capable of developing such an ability to function adequately despite high concentration of alcohol in the blood that test impairment cannot be related to tissue levels. Rosenbaum (224) also has expressed the opinion that the central nervous system can compensate to its alcoholic content but this adaptation is variable. In support of this he cites results of experiments indicating that following ingestion of alcohol a person will exhibit signs of intoxication during the period of rising blood alcohol at lower blood levels than during the "sobering up" process which may vary from 4 to 10 hours. These experiments are uncritical in that decisions are reached based only on the gross

appearance of the patient and are not subject to quantitative measurement of impairment such as can be achieved by psychometric and dexterity tests.

In contrast, examination of 6,000 brains for their alcohol concentrations has indicated that the effects of alcohol are in direct proportion to the amount present in the brain. In slight intoxication as manifested by aggressiveness and loss of care, the level falls between .1 and .25%. In cases manifest by disturbance of equilibrium, the level falls between .25 and .4%.

In an attempt to equate individual impairment, Manz (225) and several clinicians have proposed that controlled amounts of alcohol be given to a defendant in order to determine his degree of tolerance, if any, to the drug and whether or not alcohol releases specific drives or urges. The full cooperation of the defendant, while not required legally, is of utmost importance psychologically.

Despite these objections the vast majority of medical evidence points towards an excellent correlation between impairment from alcohol and its level in the breath and blood as indicated in previous chapters.

Sampling Errors

Rabinowitch (226) criticized the validity of chemical tests for intoxication, stating that faulty procedure such as sterilizing the skin with alcohol prior to taking a blood sample or making determination of the alcohol content from a clotted blood sample will lead to erroneous results. He states that the use of capillary blood is a potential source of error since the variation of the distribution of alcohol between that and venous blood is considerable. Tests conducted by Harger (227) do not confirm this finding. Exogenous alcohol of course must be excluded from the sample, but standard practices do not permit sterilization of the subject's skin or instruments with alcohol. The distribution factor is not of significance unless capillary blood is used, a practice not done to any extent in this country, and then it is of questionable significance for only a short time.

Substances Giving Erroneous Results

Using the method of Widmark (215) for analyses, blood samples were taken from patients, none of whom had alcohol or had undergone ether, chloroform or chloroethyl anesthesia. The results simulated values ranging between .02 and .05% of alcohol.

Inhalation of a gas containing 90% propane and 10% butane by guinea pigs to the point of unconsciousness gave false blood alcohol levels of .03 and .04% as analyzed by the Eidmark method. Since this exposure was considerably greater than those which could occur in practical circumstances, it was concluded that inhalation of fumes of this type do not appreciably affect alcohol concentration in the blood.

Using the method of McNally, Koehler (228) obtained endogenous alcohol levels as high as .02% in patients with severe uncontrolled diabetes mellitus. Ether and paraldehyde also were found to give positive blood alcohol estimations by this method. However no significant amounts of these or other volatile reducing substances interfering with alcohol determination are encountered in living unanesthetized patients.

Determinations for alcohol in animals exposed to benzene, benzine and a motor fuel in vapor concentrations sufficient to produce physiological symptoms gave false blood alcohol readings up to .03% with benzene, but no readings with benzine. It is assumed that the same mechanism may be obtained in humans, and that changes in the blood alcohol level of only this magnitude may occur in cases of motor fuel intoxication.

Blood alcohol concentrations determined in subjects whose back and chest were rubbed with 100 cc of 70% isopropyl alcohol showed little change above background level over a period of two hours. A level was reached as high as approximately .009%.

Occasional alterations in normal biochemistry are stated to produce substances giving false readings for alcohol.

Alterations in alkaline reserves of non-drinking patients with brain injuries did not give rise to any unusual alcohol reading nor did administration of ammonium chloride to a man whose alkali reserve had dropped to 31%.

Postmortem Factors

Turkel (229) has reviewed the occasional errors introduced by postmortem diffusion of alcohol from the stomach into the surrounding vessels. He has urged, therefore the collection of blood specimens from the femoral veins.

Dettling (230) reports that the determination of alcohol postmortem may be affected by putrefactive products and by possible postmortem diffusion of alcohol from the stomach. He suggests that muscle tissue, which is less subject to putrefaction and in which there is little chance of diffusion from

the stomach, is an ideal sample for postmortem alcohol determinations. He showed good agreement between the alcohol content of the brain and muscle in cadavers.

Methods generally used for the determination of alcohol concentration in body fluids are valid in living persons and in persons dead up to 48-96 hours, or until putrefaction sets in. At that time a variety of volatile reducing substances occur to which some methods are sensitive, and the results may be of questionable validity. Alcohol concentrations in excess of 0.5% have been observed by subjects who were known to be non-alcoholic.

Postmortem production of alcohol has been demonstrated as being due to the presence of various bacteria including Candida, albicans and saccharomyces. Under artificial in vitro conditions, pure cultures containing .1% glucose produced alcohol in amounts of .5%.

Breath Tests

There may be a greater variation in these tests than is achieved by direct blood analysis. Estimations of the level of alcohol in the blood can be made by analysis of the breath. Re-breathed and alveolar air samples give essentially the same result; the ratio of alveolar air to blood is 1:2000. In 63% of the cases the values are within 10% of the two media. Collection of air specimens in aluminum bags gives slightly better results than when rubber balloons are used. Perfect correlation cannot be expected between blood and breath alcohol because of fluctuations in breath temperature, discrepancy between alcohol and peripheral and heart blood, and the fluctuation in CO_2 content of expired air. In spite of these fluctuations, results obtained by breath analysis are considered by Harger (231) to be sufficiently accurate for practical purposes in traffic and industrial cases.

A number of substances have been claimed to give erroneous results with breath alcohol methods. Among these are acetone, citrus fruit, cheese, garlic, and onion. None has been shown to actually give a false positive reading of significance.

Legal Questions

Different countries and different jurisdictions within our country accept various levels as indicating intoxication as regards the performance of skilled tasks. An alcoholic concentration of .05% in the blood of a driver is considered evidence of being "under the influence" in Norway and the driver is subject to arrest. In France there is no legislation concerning chemical tests for alcoholic intoxication.

In most areas in the United States this level is now set at 0.15%, though there is a trend to lower this. Chemical tests have not been used in the South African courts as late as 1949 because of a common law principle which protects the accused person from giving, under compulsion, any evidence which incriminates him. Since he can consent to such a test only when he is sober, his state of intoxication nullifies the consent.

Various court decisions in the United States have held both that compulsory tests for alcoholic intoxication violate the constitutional privilege, and the opposite view. State legislation can be enacted to remove all doubt as to the legality of chemical tests and overcome the alleged existence of privilege. In some areas the privilege of using the highways is retained for persons agreeing to submit to scientific tests for alcohol intoxication.

The constitutionality of compulsory chemical tests to determine alcoholic intoxication has been reviewed and reported that in 1945 only four states had specifically legalized admission of results of chemical tests as evidence of intoxication and none of the laws provided for the compulsory taking of specimens for the tests. After reviewing the historical place of the privileged against self-incrimination in our society, Mamet (232) developed the thesis that if the use of the highways was viewed as a right and the paramount rights of the public at large in conflict of the rights of the individual, the latter must yield and "by the application of this theory the issue of self-incrimination can be easily disposed of by simply recognizing the suprior power of the sovereign."

The American Law Institute in its Model Code of Evidence rule 205, definitely takes the position that it is not a denial of the privilege to compel an accused person to submit his body for examination for the purpose of discovering or recording corporal features or other identifying chacteristics of his physical and mental condition or to furnish or permit the taking of samples of body fluid for analysis. Some courts have upheld the refusal to submit to the tests can be introduced in evidence.

The question as to whether the danger from drinking drivers warrants the curtailment of liberty of all drivers by requiring them to agree to blood alcohol tests to measure sobriety has been debated by a number of jurors. There is a tendency for courts to arrive at a consistency in their finding that intoxicated drivers are a menace and that chemical tests may aid in controlling them. However, the driver can refuse the test and therefore lose his license.

Summary

Despite the objections of a few investigators relative to the chemical tests for intoxication, it is the author's opinion that the large body of medical knowledge confirms the usefulness of these tests; that while clinical judgments formed as to the behavior of an individual through examination are sometimes clouded by the alerting effect of the incident itself, the objectivity of the chemical test commends it as a powerful factor in decisions relating to questions of sobriety, competence and probably behavior. This is particularly true providing the obtaining of a suitable specimen has been possible temporally to the event.

VIII

CHRONIC ALCOHOLISM

From our review of this subject in depth we must conclude that the chronic alcoholic is a drug addict, and certain knowledge of the condition of chronic alcoholism is germane to the effects of alcohol in the nervous system. Drug addiction may be defined as "a state in which a person has lost the power of self-control with reference to a drug, and abuses the drug to such an extent that the person or society is harmed." There are three distinct phenomena embraced within addiction, namely habituation, physical dependence and tolerance. Habituation is an emotional or psychological dependence on the drug and substitution of the drug for other types of adaptive behavior. Physical dependence refers to altered physiological states brought about through repeated taking of the drug necessitating its continual use to prevent illness termed an abstinence syndrome. Tolerance is the diminishing effect of the same dose of drug on repetitive taking. There is no question but that in chronic alcoholism both habituation and tolerance develop and, as demonstrated by Isabell (233) it is quite possible that delirium tremens is an abstinence syndrome based on physical dependence of the drug.

Utilizing withdrawal symptoms as the criteria for physical dependence, Jellinek (234) concludes that in some varieties of alcoholism there is true addiction in the pharmacological sense, and while the withdrawal syndrome culminating in delirium tremens is reinforced by symptoms which are, however, of true neurological character, still some of them are of neuroendocrine nature as well. After long and extensive bouts, this syndrome may terminate fatally and convulsions following alcohol withdrawal are truly to be considered as part of the withdrawal syndrome and not arising from alcoholic epilepsy.

Data is not available to indicate whether there is a rise or a decline in the rate of alcoholism in the United States. Referring to the years 1940 and 1948, the incidence per 100,000 population was 3,028 against 3,952. However, the rate of alcoholism per drinking population based on a Gallup poll indicates rates respectively of 6,330 and 6,140. In any case, alcoholism represents a leading and serious public health problem in the United States, as it does in most countries.

McCord (235) followed a group of subjects in a longitudinal evaluation studied in the late 30's and early 1940's and again in 1956, tracing deviant subjects through criminal courts, Alcoholics Anonymous, public and private mental health facilities. Twenty-nine of the group under study had become alcoholics, but before the onset of the disorder they did not differ from the control population in either nutritional or glandular functioning. As a group, in childhood they were not disturbed by inferiority feelings, oral tendencies or homosexual urges, but they may have been more "self destructive." It is concluded that certain ethnic groups, the American middle class, and perhaps American culture produce a tendency toward alcoholism, and conflict in familial attitudes about drinking may lend itself to alcoholism.

Jellinek (236) introduced a formula for the estimation of prevalence of alcoholism. This utilizes the reported liver cirrhosis mortality as a primary source of data and involves three factors: P, the percentage of such deaths attributable to alcoholism; K, the percentage of all alcoholics with complications who die annually from liver cirrhosis; and R, the ratio of all alcoholics to alcoholics with complications. The concept has been found useful as an attempt to meet the need for a method which is more economical and versatile in field surveys and is not subject to deficiencies of most deductive statistical approaches. A comparison with data derived independently by other means shows reasonably good agreement in most cases.

Alcoholism as a primary cause of death has a rate of 1.9; death from other causes with alcoholism as a secondary cause is 2.4; death from cirrhosis with mention of alcoholism is 1.1, giving a total rate of 5.4/100,000. Because of social considerations it is estimated that only about half the deaths due to alcoholism are so reported and the true rate is probably closer to 11.6.

In an international comparison France leads the list in death rates from acute and chronic alcoholism with 11.3 and 3.9 per 100,000 men and women respectively, followed by Switzerland and the Negro population in the United States. As regards death rates from cirrhosis of the liver, France is exceeded only by Portugal. In France the average consumption

of absolute alcohol in the 1955 period was 36 liters for men and 21 for women. Death from cirrhosis of the liver has risen markedly in France during the 30 year period of 1925 to 1955. Generally death rates from alcoholism are higher in regions where distilled spirits are drunk more freely. Application of the Jellinek formula yields 1,100,000 male and 600,000 female chronic alcoholics in France, giving rates of 77 and 38 for 1000 adults, men and women respectively.

The seriousness of the problem of the excessive drinker is not necessarily measured in terms of total incidence, since one moderate problem drinker in a key position may far outweigh in importance several advanced cases in the ranks. Due to social acceptance of drinking in moderate amounts, those who overindulge manage to get by for varying periods of time. When actual intake exceeds substantially the socially acceptable limits, the problem drinker's associates become aware of his problem. The factors then inherent in human relationships begin to play a part in hiding the actual alcoholic state. Friends and family of the potential patient do all in their power to prevent the knowledge of the problem from reaching the employer. Fellow workers invariably cover up. They fail to report tardiness, inefficiency and at times actual inebriation. The problem drinker in turn, in attempting to guard his escape mechanism, will go to any lengths to prevent detection of his condition. He denies or minimizes drinking in the face of overwhelming evidence and develops a plausible story of half truths, bland innocence and reassurance that will convince the unwary and uninformed.

Pollack (237) reported that regular and periodic abuse of alcohol leads to mental disease, that the average length of drinking episodes prior to first hospitalization was 22 years for male patients and 14 years for female, and that more mental disease occurred in the years 1936-37 which reflects the prohibition period than in the years 1920-23, which reflects the pre-prohibition period.

Fleeson (238), in a study of 289 abnormal drinkers, was able to classify them into three groups with certain significant characteristics. First, there is the primary addict who suffers from addiction from the beginning of the use of alcohol and whose drinking habits arise primarily from within the personality structure. Second, there is the symptomatic drinker whose drinking is only one of many symptoms and in whom there usually develops a well-defined clinical entity such as schizophrenia or manic-depressive states. Third, the exogenous drinker who constitutes the majority of abnormal drinkers with no single personality type and whose drinking is primarily exogenously determined. Tremendous effort has been directed towards an attempt to discover the cause of this disease.

It is concluded by a number of physicians and psychiatric specialists that addiction to alcohol is the result of a deep-seated personality disturbance. Alcohol addiction may be dependent on a number of simple factors, however, such as the psychological state of the individual resulting from his attitude toward drinking, which is a function of the environment in which he was raised, the juxtaposition of stress situations with drinking experiences in which the drinking itself is important to the individual, and the possibility that enough alcohol can be taken at times of stressful situations to permit a reduction in tension within the potential addict.

The hypothesis that inborn preference of alcohol is caused by physiological factors, that is, difference in metabolism of the animal, has been advanced by several investigators.

Williams (239) states that "inborn errors of metabolism" are commonplace, that every individual possesses a distinctive metabolic personality and that susceptibility to numerous diseases, including alcoholism and drug addiction, is greatly influenced by this individual metabolic pattern.

The genetotrophic theory of alcoholism contends that the presence of one or more partially genetic blocks leads to a distinctive production of one or more specific enzymes which result in corresponding impairment of ability to utilize one or more nutritional elements, which means that the individual has an augmented requirement for these elements and that he possesses the distinctive metabolic pattern which predisposes to alcoholism. The basis for the final step in this hypothesis has been questioned. Why a craving for alcohol should develop when the underlying deficiencies are in other substances is not satisfactorily explained.

Goldfarb (193) supports the view that in many individuals alcohol provokes an alteration of the neuroendocrine homeostasis mechanism. Alcoholism then, by this thesis, is in some persons a self-pertetuating progressive disease in which the organism invites the noxious agent because of its helpfulness in stimulating needed secretory responses of adrenal cortex and then requires the same agent with increasing constancy to achieve the desired result because of its proclivity in producing pluriglandular dysfunction.

Despite much well-directed effort and the imaginative work of R. J. Williams (239) and his associates who have championed the genetic trophic theory, there does not appear any ready explanation of the origin of this major public health and road problem.

Therapy

The clinical and pathological manifestations of chronic alcoholism, principally polyneuropathy, the alcoholic psychoses and encephalopathies, are manifestations not of direct toxic effect of alcohol but of metabolic disturbances especially a vitaminosis due to the neglect of proper diet by excessive drinkers and in complete absorption of the viatamins due to gastritis and intestinal and liver changes, especially of vitamin B_1, nicotinic acid and perhaps vitamin C. Since alcohol seems to be as firmly a part of life of mankind as its industrial and sexual habits, and since legal and educational measures are inadequate to abolish alcoholism, it is suggested that the vendors of drinks should be in a position to display legends reminding the drinkers to eat well, to supplement his food with vitamins and thereby prevent serious damage. The ingestion of heavy amounts of alcohol requires approximately 20 mg each of thiamine, nicotinic acid and ascorbic acid daily. The basic problem of chronic alcoholism itself requires a multiple approach: psychotherapy, family-oriented therapy, groups like Alcoholics Anonymous, and as an adjunct at times, agents such as TETD which prevent drinking.

Chronic alcoholics who followed a therapeutic regime of rest, vitamin supplementation, a diet of 350 gm carbohydrate, 125 gm protein and 100 gm of fat, and who discontinue their drinking will respond with disappearance of liver disease if fatty livers are the chief hepatic pathology. However, morbidity and mortality in patients with Laennec's cirrhosis, while related to the response and measures of rehabilitation, have a poorer prognosis.

Some physicians have contended that the alcoholic does not usually need to be treated in a psychiatric or special hospital, and it is not only possible but beneficial to treat him in a general hospital setting. The patient's problem is frequently not only psychiatric but medical and at times constitutes a real emergency which is better treated under this environment.

There are many drugs of the sedative and tranquilizing properties available for the use in the treatment of the hospitalized alcoholic. The ambulatory alcoholic, however, presents different problems. In a trial of reserpine it was observed that patients who were able successfully to maintain sobriety while receiving reserpine three times a day spontaneously talked about relief of anxiety. However it did seem to potentiate the effects of alcohol in patients who continued to drink while taking the medication.

The experience of "hitting bottom" is much discussed in the Alcoholics Anonymous literature and it is believed that the alcoholic is often

susceptible to therapy at this time. Smith (240) utilized the hallucinogenic drug, LSD, in doses of 200 to 400 μg, and mescaline in doses of .5 gm to produce an artificial "bottom." Half the patients thus treated who, in addition were given intensive psychotherapy and rehabilitative measures, were felt to be improved by this total approach.

Treatment of chronic alcoholism by pentothal narcosis in combination with condition-reflex treatment has been reported especially successful in alcoholic patients who drink primarily to relieve tension or emotional distress and who present psychopathic personality traits or history of neurosis or psychosis.

Pyrahexyl, a marijuana-like compound, produces amelioration of typical post-alcoholic symptoms including tremulousness, restlessness, apprehension and anorexia in 84% of treated patients. Side effects such as mild headache and minimal ataxia were few and there were no withdrawal symptoms.

Duress in some form and degree is instrumental in leading many patients to accept treatment. Just how and when duress can be judiciously applied is a delicate problem. If applied too early or too forcibly the patient may react with increased rationalization in defense and further delay his facing realities of the drinking problem, and should it be applied too mildly there may be too little left to salvage. Factors involving duresses are threatened loss of job, family, security, physical and mental health, and the respect of associates.

Alcoholics are prone to taking excessive amounts of sedatives, and meprobamate has been reported to cause addiction in six patients who had previously been addicted to either alcohol or barbiturates. Withdrawal symptoms have been recorded by Lemere (241) as occurring after discontinuance of this drug. Tolerance also occurred with meprobamate so that up to 20 tablets per day are required to obtain a depressant effect and on removal, severe withdrawal symptoms requiring hospitalization have occurred. Increasing anxiety has also been reported in alcoholics who have been administered chlorpromazine in increasing doses until up to 800 mg daily has been taken. All sedative drugs are potentially dangerous to the alcoholic.

Voegtlin (242) carried on a six month study evaluating the effect of ACTH and adrenal steroids on the lapse rate in chronic alcoholics. The medications were given as follows: adrenal steroid in the form of Cortone, 25 mg four times daily, and ACTH, 1 cc daily. This was given in a cyclic schedule: the adrenosteroid medication for 28 days, a rest period of 7 days; ACTH for 3 days and a final rest period of 7 days with completion of

the cycle. After treatment all patients were improved in their subjective feelings but this varied in both degree and direction. Laboratory studies did not indicate any abnormalities of adrenal activity or functions typical of alcoholics. Of the patients, 40% remained abstinent for up to 12 months and 18% for 18 months. It was concluded that adrenal therapy will be of little specific value except as an adjunct to the existing methods of treating chronic alcoholism. Five of 36 patients developed psychotic reactions to the drugs administered.

Glutamine has been reported as appreciably decreasing voluntary alcohol consumption in a group of alcohol addicts. However when placebos were given in place of glutamine, the beneficial effects continued for as long as three months. However, no subject showed a response to placebo unless he had first been given glutamine.

Gross (243) has postulated the fact that chronic alcoholism either by the direct action of alcohol or through its concomitant deficiencies in vitamins has a deleterious effect upon pituitary and that the effects seen such as inhibition of growth, amenorrhea, impotence, testicular atrophy, tremor, perspiration, diuresis and heat loss, may be due to inhibition of this endocrine secreting gland.

Wellman (244) recommends that a serviceman who has reached the stage of chronic alcoholism where he drinks to block out the frustration and pain brought on by previous drinking should not be discharged, but treated as for any other disease. In his experience one-fifth of men in the service referred for alcoholism can be helped to become temperate drinkers; however, once loss of control and lower tolerance to alcohol sets in, total abstinence is the only solution.

Money saved in rehabilitating 50% of the Air Force personnel treated through an experimental program launched in the 3700 USAF hospital, saved a calculated 1, 000, 000 dollars in terms of the cost of training different grades involved. Military services were urged to utilize the latest advances in medical and social methods for treating alcoholism, using referal and self-referal for prompt evaluation and more flexible, rapid means of disposition within the framework of existing regulations.

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consider information which would be requisite to an experimental investigation of the problem. Special attention was directed toward the pharmacology, physiology, effects on the nervous system, and behavior following acute or repeated intake of alcohol. Numerous observations have been made regarding the effect of alcohol alone. Relatively few have been made concerning the combinations of alcohol with other drugs. Practically no information was available concerning the effect of the environment, drugs and chemicals, especially as regards reduced temperatures. Based on the literature review, a narrative description of the material necessary to evaluate the original problem was made and recommendations were set forth for an experimental program which would obviously have to be carried over some period of time in order to clarify the many undetermined factors relating to the effects of alcohol alone and in combination with other drugs as influenced by reduced ambient temperatures.

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13. ABSTRACT This review of medical and scientific literature was undertaken to establish what knowledge was existent regarding effects of alcohol and other drugs in the presence of reduced environmental temperatures on the behavior of animals and man. The gathering, classifying, and reviewing of this literature was necessary to determine whether further work should be done in this area. The paramount problem was to determine whether reduced environmental temperatures such as might be expected in environments in which Air Force personnel would be operating in their world-wide mission were a factor which should be considered in predicting behavior, following the ingestion of alcohol, taking of drugs or exposure to other agents which might have effects on the central nervous system. This review was accomplished in part by direct reference to journals dealing with the action of drugs and environmental agents, and in part by reference to standard abstracting sources. Special attention was paid to material appearing in the Quarterly Journal of Studies on Alcohol. Wherever the subject matter seemed of sufficient importance to require critical review of original data, the original articles were sought out and analyzed. In all, more than 4, 500 articles and abstracts were read. Of these, 1200 were selected as being especially pertinent and 700 of these were carefully reviewed. A cross-index was prepared according to major topic headings. Due to the paucity of material pertaining to the subject of the environment, the original scope of the project was enlarged to

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